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Therapeutic management of inflammatory heart diseases

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ABSTRACT

Inflammatory heart diseases include a wide range of clinical entities whose manifestations largely depend on whether the pericardium, myocardium, and/or endocardium are affected by infectious agents or sterile inflammation. Advancements in understanding the inflammatory pathogenesis of pericarditis have led to the successful development of targeted anti-inflammatory therapies. While non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine remain first-line therapeutic options in those with acute pericarditis, interleukin-1 (IL-1) inhibitors have been recently approved for the treatment of recurrent/refractory pericarditis. Myocarditis is currently managed with supportive care, with glucocorticoids and immunosuppression being considered for virus-negative cases, especially when cardiac function is depressed or in cases of known underlying autoimmune disease. Coronary involvement may occur in systemic vasculitides – including Kawasaki disease (up to 20% of

Abbreviations: ACC, American College of Cardiology; AIRTRIP, Anakinra-Treatment of Recurrent Idiopathic Pericarditis; ANCA, anti-neutrophil cytoplasmic autoantibody; AOSD, adult-onset Still's disease; ARAMIS, Anakinra versus placebo double-blind Randomized controlled trial for the treatment of Acute MyocarditIS; ARCHER, CardiolRx on Myocardial Recovery in Patients With Acute Myocarditis; ASA, acetylsalicylic acid; BS, Behçet's syndrome; CAPS, cryopyrin-associated periodic syndromes; CBD, cannabidiol; CD, cluster of differentiation; CHASM-CS-RCT, Cardiac Sarcoidosis Multi-Center Randomized Controlled Trial; CMP-MYTHiC, CMP-MYTHiC Trial and Registry - CardioMyoPathy With MYocarditis THerapy With Colchicine; CMR, cardiac magnetic resonance; COVID-19, coronavirus disease 2019; CREST, calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia; CRP, C-reactive protein; CV, cardiovascular; DAMP, damage-associated molecular pattern; DIRA, deficiency of IL-1 receptor antagonist; DMARD, disease-modifying anti-rheumatic drug; EGPA, eosinophilic granulomatosis with polyangiitis; EMB, endomyocardial biopsy; ESC, European Society of Cardiology; EULAR, European League Against Rheumatism; FDA, Food and Drug Administration; FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography; GCA, giant cell arteritis; ICD, implantable cardioverter defibrillator; ICI, immune checkpoint inhibitor; IFN-γ, interferon-gamma; IL-1, interleukin-1; IMPROVE-MC, Study to Evaluate the Efficacy of Immunosuppression in Myocarditis or Inflammatory Cardiomyopathy; IVIG, intravenous immunoglobulins; J-ACNES, Japanese Antibacterial Drug Management for Cardiac Sarcoidosis; LV, left ventricle; LVEF, left ventricle ejection fraction; MAGiC- ART, Multimodality assessment of granulomas in cardiac sarcoidosis: Anakinra Randomized Trial; MAS, macrophage activation syndrome; MIS-A, multi-inflammatory syndrome in adults; MIS-C, multi-inflammatory syndrome in children; MYTHS, MYocarditis THerapy With Steroids; NBTE, non-bacterial thrombotic endocarditis; NF-κB, nuclear factor kappa-light-chain enhancer of activated B cells; NLRP3, NACHT, leucine-rich repeat and pyrin-domain containing protein 3; NRS, numerical rating scale; NSAID, non-steroidal anti-inflammatory drug; PAMP, pathogen-associated molecular pattern; PAN, polyarteritis nodosa; PRR, pattern recognition receptor; RA, rheumatoid arthritis; RHAPSODY, Rilonacept Inhibition of Interleukin-1 Alpha and Beta for Recurrent Pericarditis: a Pivotal Symptomatology and Outcomes Study; RNA, ribonucleic acid; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; TAK, Takayasu arteritis; TGF-β, transforming growth factor-β; TLR, toll-like receptor; TNF, tumor necrosis factor.

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affected subjects), Takayasu arteritis (10–30%), polyarteritis nodosa (50%), and giant cell arteritis (<1%). Treatment of coronary arteritis generally includes high-dose glucocorticoids, followed by immunosuppressive drugs. Non-infective endocarditis may present in association with cancer or autoimmune disorders, such as systemic lupus erythematosus (Libman-Sacks endocarditis). Management of non-infective endocarditis generally encompasses treatment of the underlying disease, including surgery in selected cases. Cardiac imaging, particularly cardiac magnetic resonance and ^{18}F-fluorodeoxyglucose positron emission tomography, are helpful for non-invasive tissue evaluation and areas of high metabolic activity, respectively. Newer techniques, such as fat attenuation index, are likely to be further additive and may reduce diagnostic delay of coronary inflammation. In the above-mentioned conditions, targeted anti-cytokine therapies can selectively address key pathogenic mechanisms more safely and effectively than broad, nonselective immunosuppressants. Additional research is needed to establish novel molecular targets and improve phenotyping and risk stratification of patients with inflammatory heart diseases, ultimately enabling precision and personalized treatment approaches.

1. Introduction

The inflammatory response is a physiological and evolutionarily conserved host immune response against a wide range of *noxae* that aims to clear detrimental stimuli and restore tissue integrity following injury (Libby et al., 2024). While finely tuned at both intra- and inter-cellular levels, dysregulated inflammatory responses cause undesired additional tissue injury and favor the development of inflammatory disorders (Coggins & Rosenzweig, 2012). The innate and adaptive immunity responds to cardiac injury caused by pathogens or any environmental stimulus (Wang et al., 2025). Resident cardiac immune cells are triggered by the detection of pathogen-associated molecular patterns (PAMPs) – mainly bacteria or viruses – or damage-associated molecular patterns (DAMPs) – dying or injured myocardial cells (Epelman, Liu, & Mann, 2015), with the latter starting an inflammatory response referred to as "sterile inflammation," i.e. tissue injury occurs without a known pathogenic infection (Matzinger, 1994). Whatever the cause is, a rapid recruitment of neutrophils and macrophages at the site of injury occurs (Epelman et al., 2015). Pattern recognition receptors (PRRs) encountering DAMPs and PAMPs cause the release of a number of interleukins, that are master regulators of the inflammatory response, often possessing complementary or antagonizing functions, as some exert pro-inflammatory effects (e.g., interleukin-1β [IL-1β] and IL-6). In contrast, other cytokines promote inflammation resolution (e.g., IL-10 and transforming growth factor-β [TGF-β]) (Dinarello, 2019; Mantovani, Dinarello, Molgora, & Garlanda, 2019). Interleukins are often pleotropic with context-specific functions, such as pro- or anti-inflammatory signaling on IL-6 pending on the context (Preda et al., 2026; Tanaka, Narazaki, & Kishimoto, 2014). To this end, a central role is played by the NACHT, leucine-rich repeat and pyrin-domain containing protein 3 (NLRP3) inflammasome, a macromolecular protein that has evolved to activate inflammatory caspases, where caspase-1 is the effector enzyme that in humans promotes the maturation and secretion of pro-inflammatory cytokines, such as IL-1β and IL-18, and a form of inflammatory, lytic cell death, i.e. pyroptosis (Toldo & Abbate, 2024). Its role is now recognized both in ischemic and non-ischemic cardiac injury.

Inflammatory heart diseases include a wide range of disorders whose etiology is various, including infectious, autoimmune, auto-inflammatory, toxic, or allergic causes. The pericardium and the myocardium are more frequently involved leading to pericarditis and myocarditis, respectively (Del Buono et al., 2024) (Fig. 1). However, the endocardium can also be subjected to inflammation – endocarditis, driven by infectious and non-infectious stimuli. Coronary vessels, the aorta, and its main branches may also become inflamed when involved in a systemic inflammatory process – vasculitis (Pagnoux & Guillevin, 2005; Roldan et al., 2013) (Fig. 1). The increased inflammatory burden in rheumatological disorders impairs the innate and adaptive immune responses, thus worsening the risk of atherosclerosis and other adverse cardiovascular (CV) events (Weber et al., 2023). Atherosclerosis is also an inflammatory process, and novel metrics of coronary CT imaging assessing adipocyte biology or invasive techniques with optimal coherence tomography enable visualization of this process (Markousis-Mavrogenis et al., 2025). Accordingly, the field of cardio-rheumatology/cardio-immunology is continuously expanding in that a multidisciplinary approach is necessary to best manage clinical outcomes and long-term survival (Abbate, Weber, Garschick, Adamo, & Beavers, 2024; Weber, Garshick, Abbate, et al., 2023; Weber, Garshick, Liao, & Di Carli, 2023).

It is, however, important to briefly clarify the concepts of autoimmunity and auto-inflammation in the field of the inflammatory diseases of the heart while referring readers elsewhere (Dinarello, 2011) for an exhaustive overview on this topic. Autoimmune diseases are characterized by an imbalance in the responses of the adaptive immune system

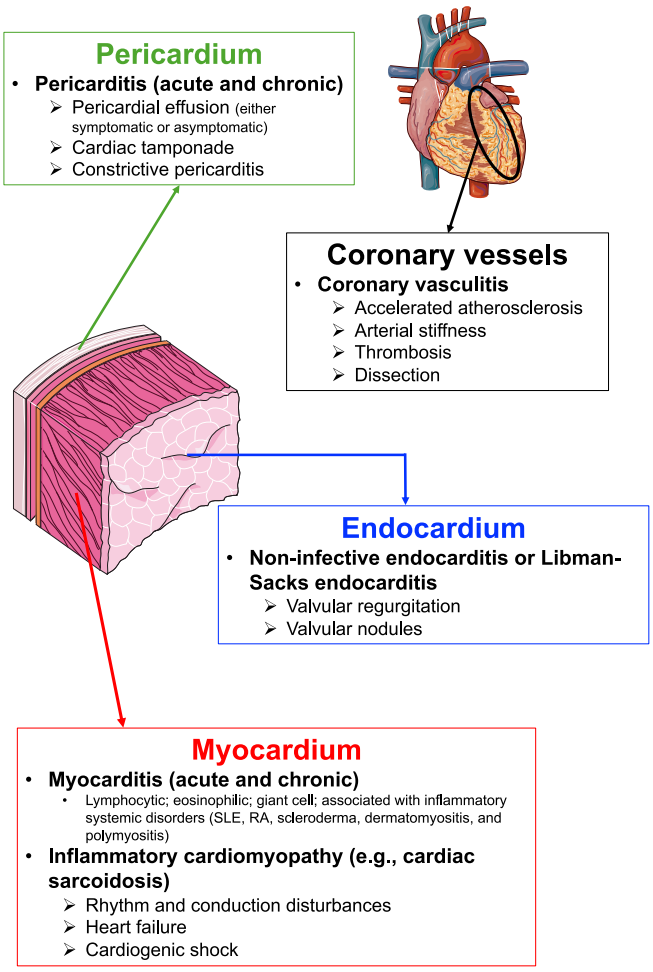


Fig. 1. Cardiovascular involvement of systemic inflammatory disorders. Autoimmune and inflammatory/auto-inflammatory systemic diseases may involve any part of the heart and cause different clinical manifestations.

and by the production of autoantibodies or the activation of autoreactive T cells. Autoinflammatory disorders typically present with cyclic flares of inflammation, either local or systemic, rather than progressive inflammation, and some of them are caused by genetic defects in innate inflammatory pathways that manifest early in life. In addition, they do not show any associations with human leukocyte antigen or major histocompatibility complex haplotypes, and no autoreactive T cells or autoantibodies are encountered. The clinical presentation of autoimmune disorders is often driven by the tissue injury caused by the inflammatory process, while for autoinflammatory diseases symptoms are caused by the systemic release of pro-inflammatory cytokines. Despite this, it may occur that some systemic inflammatory diseases are primarily caused by autoinflammatory mechanisms, but dysregulated pathways in the adaptive response may account for their pathogenesis (Dinarello, 2011).

This review summarizes the current therapeutic management of main inflammatory heart diseases (Fig. 2), highlighting major knowledge gaps, unmet clinical needs and research efforts.

2. Pericarditis

Pericarditis – the inflammation of the serosal sac surrounding the heart – is the most frequent pericardial disease (Cremer, Klein, & Imazio, 2024). Diagnosis of pericarditis is based on 2025 European Society of Cardiology (ESC) criteria, where two or more of the following four criteria must be met: pericardial chest pain, pericardial rubs, electrocardiogram changes (new, widespread ST-segment elevation and/or PR segment depression), new or worsening pericardial effusion, pericardial edema or injury at cardiac magnetic resonance (CMR), and/or elevated C-reactive protein (CRP) (Schulz-Menger et al., 2025). A recent Consensus released by the American College of Cardiology (ACC) emphasizes chest pain as the main symptom along with other criteria, whose presence makes the diagnosis possible (one in addition to chest pain) or definite (two in addition to chest pain) (Wang et al., 2025). Pericarditis is characterized by a rather benign course following a therapeutic regimen based on non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine (Chiabrando et al., 2020; Klein et al., 2024). While most cases are considered idiopathic, pericarditis may also present as a manifestation of a systemic autoimmune or rheumatological disorder (especially systemic lupus erythematosus [SLE], rheumatoid arthritis [RA] or systemic sclerosis) (Aikawa et al., 2024; Malandrino, Weber, Garshick, & Abbate, 2024), in the setting of an autoinflammatory disease, such as familial Mediterranean fever (Kawano et al., 2024; Kees et al., 1997), or it may be caused by infections, mainly viruses in developed countries and tuberculosis in developing countries (Adler et al., 2015). Complications, such as cardiac tamponade, constrictive pericarditis, and recurrences, may occur in a significant proportion of patients, with recurrences being the most frequent ones (15 to 30% of patients) that substantially worsen patient's quality of life (Thomas et al., 2024; Vecchie et al., 2020) and may occur even after an initial uncomplicated course (Del Buono et al., 2021). It is important to assess for myocardial involvement during pericarditis, i.e. myopericardial syndrome, as the presence of myocardial injury is associated with an increased risk of heart failure and arrhythmias, and requires a targeted management plan (see Myocarditis section) (Schulz-Menger et al., 2025).

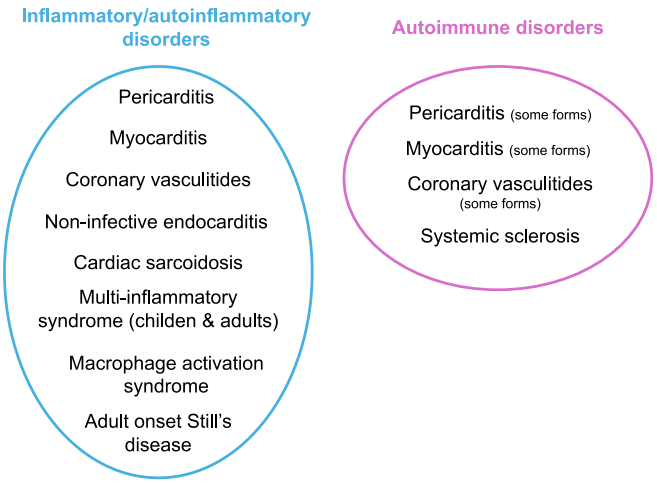


Fig. 2. Main disease mechanisms of inflammatory heart diseases. While most inflammatory heart diseases have distinct disease mechanisms (inflammation/autoinflammation vs. autoimmunity), it may occur that some systemic inflammatory diseases primarily caused by autoinflammatory mechanisms may present dysregulated pathways in the adaptive response.

The pathophysiology of pericarditis has been largely investigated over recent years (Bonaventura et al., 2023). It is now recognized that the NLRP3 inflammasome/IL-1β axis plays a key pathogenic role (Mauro et al., 2021), portending relevant therapeutic implications. Idiopathic pericarditis can develop after the release of DAMPs or PAMPs, activating toll-like receptor (TLRs) and inducing the translocation of nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB) to the nucleus, where it promotes the transcription of genes encoding for NLRP3 inflammasome core components and effectors (e.g., pro-caspase-1). Following assembly and activation, the NLRP3 inflammasome processes the cleavage of pro-IL-1β into biologically active IL-1β, which in turn amplifies the inflammatory response in a feed-forward loop, promoting a vicious inflammatory circle that characterizes the recurrent pericarditis phenotype (Dinarello, 2010). Conversely, pericarditis in autoimmune or rheumatic diseases usually manifests as a systemic rather than a local process involving diverse tissues, including serous membranes. Once self-antigens are exposed due to pericardial damage, T and B cells produce autoantibodies responsible for initiating and sustaining the autoimmune process (Bonaventura et al., 2021; Caforio et al., 2010). Secondary activation of the innate immune response may amplify and perpetuate injury in the autoimmune forms of pericarditis.

According to current ESC guidelines (Schulz-Menger et al., 2025) and the ACC consensus paper (Wang, Klein, et al., 2025), NSAIDs and colchicine are recommended as first-line agents in patients with idiopathic forms of pericarditis (Schwier, Cornelio, Greenlee, Smith, & Wohlford, 2024). Glucocorticoids represent second-line therapies in case of insufficient response to first-line agents, although use is associated with substantial risks of recurrences (up to 4 times) and hospitalization, especially when administered at high doses (1 mg/kg/day) (Imazio et al., 2008). In patients with systemic autoimmune diseases, pericardial involvement can be either asymptomatic (e.g., isolated pericardial effusion) or symptomatic (acute pericarditis, possibly with pericardial effusion). In this case, management should be directed to increase the standard treatment for the underlying disease. Some patients may benefit from a course of NSAIDs and colchicine, and most require glucocorticoids (Adler et al., 2015; Chiabrando et al., 2020).

Given the role of the NLRP3 inflammasome/IL-1β axis in the pathogenesis of recurrent pericarditis, multiple randomized clinical trials evaluating different IL-1 blockers have been recently conducted (Imazio & Abbate, 2022; Imazio et al., 2022) (Table 1). Based on the positive results of such trials, IL-1 blockers – anakinra, rilonacept, and goflikicept (a heterodimer fusion protein functioning as a trap for both IL-1α and IL-1β) – should be considered in patients with either contraindications to or refractory to glucocorticoids, or in those presenting high-risk features, such as multiple recurrences, markedly increased CRP or extensive inflammatory involvement upon CMR in which a prolonged therapeutic course is expected (Del Buono et al., 2024; Klein et al., 2024) (Fig. 3). The most well-studied IL-1 inhibitor, anakinra, was the first to show an improvement in symptoms and reduce recurrences among difficult-to-treat cases in observational studies (Jain et al., 2015; Shaukat, Singh, Davis, Torosoff, & Peredo-Wende, 2020) as well as in acute pericarditis (Wohlford et al., 2020). The Anakinra-Treatment of Recurrent Idiopathic Pericarditis (AIRTRIP) was the first trial that evaluated anakinra

Table 1
Overview of available IL-1 blockers for recurrent pericarditis.

	Anakinra	Rilonacept	Goflikicept
Mechanism of action	Recombinant human IL-1 receptor antagonist	Chimeric fusion protein acting as a soluble decoy that binds IL-1α and IL-1β	Heterodimer fusion protein binding both IL-1α and IL-1β
Dosing	2 mg/kg daily (max 100 mg daily)	Loading dose 4.4 mg/kg (up to 320 mg, divided into 2 doses of 160 mg in 2 different sites), followed by 2.2 mg/kg (up to 160 mg) weekly	Loading dose of 160 mg at week 0, 80 mg at week 1, and 80 mg at week 2 followed by 80 mg every 2 weeks
Route of administration	Subcutaneous	Subcutaneous	Subcutaneous
RCT	AIRTRIP (Brucato et al., 2016)	RHAPSODY (Klein et al., 2021)	Goflikicept RCT (Myachikova et al., 2023)
Common adverse events	▪ Injection site reactions ▪ Risk for bacterial infections (cellulitis, bone and joint infections, and pneumonia) ▪ Hepatitis	▪ Injection site reactions ▪ Risk for bacterial infections (cellulitis, bone and joint infections, and pneumonia) ▪ Hyperlipidemia ▪ Neutropenia	▪ Injection site reactions ▪ Upper respiratory infections ▪ Blood lipid disorders
Additional information	• Progressive tapering across at least 3 months is suggested to reduce the risk of recurrences (Imazio et al., 2020) • A common scheme for anakinra tapering is to reduce by 100–300 mg/week every 1–2 months	• Progressive tapering suggested after 6 months of controlled symptoms • Suspension of rilonacept was associated with an increased rate of recurrences (Imazio et al., 2024) • Only FDA-approved IL-1 blocker for recurrent pericarditis	• Open-label long-term extension study ongoing

FDA: Food and Drug Administration; IL-1: interleukin-1; IL-1α: interleukin-1α; IL-1β: intereukin-1β.

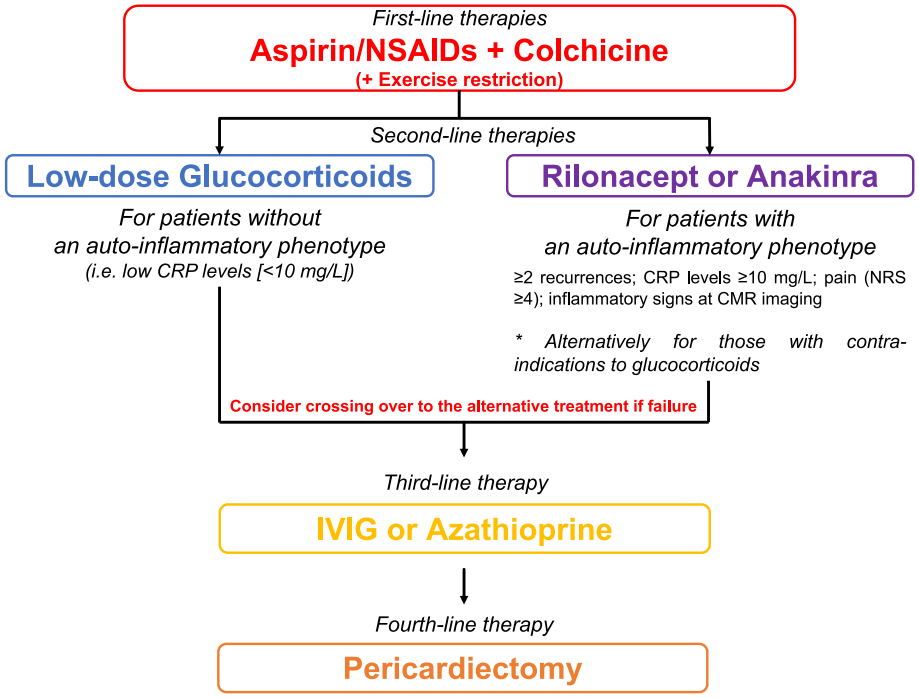


Fig. 3. Flowchart for the treatment of recurrent/refractory pericarditis. While nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine remain the mainstay for the treatment of acute and recurrent pericarditis, in case of recurrent/refractory pericarditis it is important to phenotype the patient in order to choose the best treatment.
Legend. CMR: cardiac magnetic resonance; CRP: C-reactive protein; IL-1: interleukin-1; IVIG: intravenous immunoglobulins; NRS: numerical rating scale; NSAIDs: nonsteroidal anti-inflammatory drugs. Reproduced with permission from Del Buono et al. (Del Buono et al., 2024).

in patients with recurrent pericarditis (≥3 flares) who were resistant to colchicine and dependent on glucocorticoids showing reduced recurrence rates compared with placebo (18.2% and 90%, respectively) and significantly prolonging the recurrence-free period (Brucato et al., 2016). The Rilonacept Inhibition of Interleukin-1 Alpha and Beta for Recurrent Pericarditis: a Pivotal Symptomatology and Outcomes Study (RHAPSODY) trial tested rilonacept, a chimeric fusion protein binding both IL-1α and IL-1β already approved by the Food and Drug Administration (FDA) for the treatment of cryopyrin-associated periodic syndromes (CAPS) and deficiency of IL-1 receptor antagonist (DIRA) (Klein et al., 2021). In this study, enrolling patients with ≥2 recurrences while on treatment with NSAIDs, colchicine or oral glucocorticoids in any combination, rilonacept rapidly resolved the acute flare, enabling successful weaning of background medications. Rilonacept significantly decreased the recurrence rate by 96% as compared with placebo (Klein et al., 2021). The results of the long-term extension of the RHAPSODY study (24 additional months of open-label treatment) found that continued rilonacept treatment provides persistent reduction in the risk of recurrences at 18 months, while drug suspension was associated with pericarditis recurrence in many cases (Imazio et al., 2024). More recently, goflikicept demonstrated meaningful benefits among individuals with idiopathic recurrent pericarditis in reducing recurrences

after suspension of NSAIDs, colchicine, or glucocorticoids (Myachikova et al., 2023). Fava et al. reported on the use of rilonacept in 4 women with refractory lupus pericarditis (two of them previously treated with anakinra) with complete resolution of pericarditis in 3 patients and partial resolution within 2 weeks from the first dose in the remainder (Fava, Cammarata, & Adamo, 2024). The role of IL-1 inhibition in autoimmune pericarditis and interactions between the disease-specific therapies – which can in certain scenarios induce a drug-induced pericarditis – still remains to be elucidated (Cafarelli et al., 2021; Creechan, Lockwood, Weber, Klein, & Haider, 2025; Fava et al., 2024; Oliveira Pinheiro, Seabra Rato, Madureira, Paiva, & Costa, 2022).

Cannabidiol (CBD) – a small, lipophilic, non-psychoactive compound of *Cannabis sativa* with anti-inflammatory properties (Martinez Naya et al., 2023) – was evaluated in a pre-clinical study in which it blunted IL-1β secretion by macrophages in vitro and reversed typical findings of pericardial inflammation (effusion and thickness) in a mouse model of acute pericarditis (Martinez-Naya et al., 2022). Following these encouraging findings, the phase 2 MAvERIC-Pilot study (Impact of CardiolRx™ on Recurrent Pericarditis, NCT05494788) assessed the safety/tolerance of oral CBD on top of NSAIDs, colchicine, or glucocorticoids and the improvement in chest pain after 8 weeks of treatment in 27 patients with symptomatic recurrent pericarditis ($\geq$2 recurrences and a numerical rating scale [NRS] pain score $\geq$ 4, CRP $\geq$ 10 mg/L or evidence of pericardial inflammation at CMR). Recently, interim results were presented (Cardiol Therapeutics Announces Positive Topline Data from its Phase II MAvERIC-Pilot Study Investigating CardiolRx(TM) for Recurrent Pericarditis, 2026; Luis et al., 2024). The primary endpoint of patient-reported pericardial pain showed a mean reduction of 3.7 on the NRS score after 8 weeks of treatment. In addition, 80% of patients with a baseline CRP $\geq$ 10 mg/L normalized this biomarker (from 57 mg/L at baseline to 3 mg/L) at 8 weeks. The MAVERIC-2 (CardiolRx in Recurrent Pericarditis Following IL-1 Blocker Cessation; NCT06708299) is a randomized, double-blind, placebo-controlled phase II/III trial that will be conducted in nearly 110 patients with stable, recurrent pericarditis after treatment with IL-1 blocker. Patients will be randomized to either CardiolRx™ or placebo after cessation of the IL-1 blocker with the primary clinical objective of assessing the impact of CBD on freedom from a new flare of recurrent pericarditis. It is important to remember that CBD interacts with NSAIDs (naproxen, in particular) and glucocorticoids (hydrocortisone, prednisolone) potentiating their effects (Wilson-Morkeh, Al-Abdulla, Sien, Mohamed, & Youngstein, 2020), thus patients should be closely supervised when CBD is prescribed in association with these drugs.

3. Myocarditis

Myocarditis is an inflammatory process involving the myocardium generally sustained by immune system activation causing cardiomyocyte injury. Myocarditis may manifest with chest pain, palpitations, dyspnea, fatigue, or syncope, and usually follows a relatively benign prognosis. Patients presenting isolated chest pain (in the absence of other symptoms) tend to follow a more benign disease course compared with those presenting with dyspnea or arrhythmias (Cannata et al., 2022). However, up to 25% of patients with myocarditis develop complications due to left ventricle (LV) systolic dysfunction, malignant arrhythmias, or cardiogenic shock requiring inotropes or mechanical circulatory support, which may lead to need for heart transplantation and cardiovascular (CV) death (Ammirati et al., 2018). Most frequent etiologies of myocarditis include infection, autoimmune and rheumatologic disorders and exogenous irritants, such as drugs (e.g., chemotherapy and immune checkpoint inhibitors) and vaccines (Ammirati & Moslehi, 2023; Basso, 2022; Ferone et al., 2024). In many cases, however, no apparent cause is found.

According to the World Health Organization definition, myocarditis is an inflammatory disease of the myocardium diagnosed by histological (Dallas criteria: histological evidence of inflammatory infiltrates within the myocardium associated with myocyte degeneration and necrosis of non-ischemic origin), immunological, and immunohistochemical ($\geq$14 leucocytes/mm^2 including up to 4 monocytes/mm^2 with the presence of cluster of differentiation (CD)3$^+$ T-lymphocytes $\geq$7 cells/mm^2) features accompanied by non-ischemic cardiomyocyte damage (Aretz et al., 1987; Richardson et al., 1996). Diagnosis should be primarily made on the Dallas criteria based on endomyocardial biopsy (EMB) findings (Caforio et al., 2013; Writing et al., 2025). CMR is currently used to as the preferred modality to diagnose myocarditis when the patient is clinically stable, enabling further cardiac tissue characterization and disease monitoring over time for scar formation and long-term sequelae. The diagnosis of myocarditis upon CMR is defined by the Lake Louise criteria, including edema on T2-weighted image, mapping findings and myocardial injury on late gadolinium enhancement, T1 mapping, and increased extracellular volume (Ferreira et al., 2018; Schulz-Menger et al., 2025; Writing et al., 2025). Echocardiography and increased myocardial necrosis biomarkers (i.e, high-sensitivity troponin T or I) further support the diagnosis of acute myocarditis (Schulz-Menger et al., 2025). Diagnostic criteria for clinically-suspected myocarditis have been proposed (Schulz-Menger et al., 2025). Since histopathology is not immediate and patients often need empirical therapy, it is mandatory to further evaluate approaches that incorporate multi-modality imaging and systemic biomarkers.

The pathogenesis of myocarditis is an inflammation-driven injury to the myocardium, generally attributed to an impairment of the innate and adaptive immunity (Basso, 2022; Golino et al., 2024). After recognizing a stimulus (either infectious or sterile), the innate immune system triggers an initial inflammatory response. Furthermore, dysregulation in immune tolerance, adaptive immune system can target antigens expressed on cardiomyocytes, triggering an autoimmune response that aggravates cardiac damage and dysfunction (Huang, Vallejo, Kollias, & Mann, 2009). Preclinical studies have demonstrated a pathogenic role for the NLRP3 inflammasome and IL-1β (Al-Kofahi et al., 2018; Liu et al., 2022; Miteva et al., 2018; Sun, Yuan, & Zhao, 2022; Wang, Gao, & Xiong, 2014; Zhang et al., 2018) and, to a lesser extent, interleukin-18 (IL-18) (Chang et al., 2014; Kanda et al., 2000; Liang et al., 2023). Pappritz et al. described the beneficial effect of the nonselective NLRP3 inflammasome inhibitor colchicine in a mouse model of acute myocarditis (Pappritz et al., 2022). Cardiac antigens or viral proteins can stimulate the formation of self-reactive T and B cells through molecular mimicry, leading to loss of immune tolerance. Myocardial inflammation and cardiomyocyte injury resolve in many cases through various mechanisms, including regulatory T cells (Golino, Harding, et al., 2024; Tschope et al., 2021).

Despite an improved understanding of pathogenic mechanisms from preclinical studies (Golino, Harding, et al., 2024), fewer advancements have been accomplished in the therapeutic management of patients with myocarditis (Table 2). The mainstay of treatment remains supportive care, including HF-directed therapies, treatment of arrhythmias, and etiology-specific therapy, if indicated and treatment of the underlying autoimmune condition, e.g. SLE if identified (Caforio et al., 2013). Furthermore, glucocorticoids are recommended in selected patients including those with giant cell myocarditis or eosinophilic myocarditis, and often utilized in hemodynamically unstable patients, preferably after excluding active viral replication (Ammirati et al., 2020; Basso, 2022). Data regarding pharmacological interventions targeting adaptive immunity in patients with myocarditis are limited and include broad immunosuppressive agents, as summarized in Table 2. The MYocarditis THerapy With Steroids (MYTHS; NCT05150704) is an ongoing phase 3, single-blind, randomized placebo-controlled trial testing whether pulsed intravenous methylprednisolone (1 g daily for 3 days) on top of standard therapy in patients with complicated myocarditis reduces the composite of all-cause mortality, heart transplantation, long-term LV assisted device implant, need for upgrading the temporary mechanical cardiac support, ventricular arrhythmias, first HF rehospitalization, or cardiac rhythm disturbances such as ventricular arrhythmia or atrioventricular

Table 2
Clinical trials with immunosuppressive treatments for acute myocarditis.

Authors, reference	Number of patients	Inclusion criteria	Treatment	Main findings
Mason et al. (Mason et al., 1995)	111	Histologic evidence of myocarditis and chronic HF with LVEF <45%	• SOC + cyclosporine (5 mg/kg twice daily for 24 weeks) and prednisone (1.25 mg/kg daily, then tapered until week 24) • SOC + azathioprine (1 mg/kg twice daily for 24 weeks) and prednisone (same as above) • SOC alone	No significant differences in LVEF at weeks 28 and 52 nor in the survival at one year.
Wojnicz et al. (Wojnicz et al., 2001)	84	Chronic HF due to biopsy-proven inflammatory DCM and LVEF ≤40%	• SOC + prednisone (1 mg/kg daily, then tapered until day 90) and azathioprine (1 mg/kg daily for 100 days) • SOC + placebo	• No significant differences in the primary endpoint (death, heart transplantation, and hospital readmission) at 2 years • LVEF improvement early after 3 months (95% CI: 4.2 to 13.1, $p < 0.001$) and persisting up to 2 years (95% CI: 6.94 to 19.04, $p < 0.001$) in the immunosuppression group.
Frustaci et al. (Frustaci, Russo, & Chimenti, 2009) Chimenti et al. (Chimenti, Russo, & Frustaci, 2022)	85	Chronic HF with LVEF ≤40% unresponsive to conventional supportive therapy due to biopsy-proven, virus-negative active lymphocytic myocarditis	• Azathioprine (2 mg/kg daily for 6 months) + prednisone (1 mg/kg daily for 4 weeks then tapered for 5 months) + SOC • SOC + placebo	• LVEF improvement in the treatment arm after 6 months (26.5 ± 6.7% ➔ 45.6 ± 9.6%) translated into improved NYHA class and no hospitalizations for WHF. • LVEF improvement persisted for 20 years (HR 7.24, 95% CI: 3.05 to 17.18) • Reduced risk of CV death and heart transplantation for the treatment group across a 20-year follow-up (HR 6.77, 95% CI 2.36 to 19.45 and HR 7.92, 95% CI 1.80 to 34.88, respectively).
McNamara et al. (McNamara et al., 1997)	10	Chronic HF with LVEF <40% with biopsy-proven myocarditis	• IVIG (2 g/kg daily over 2 days) + SOC	• Improvement in LVEF (from 24 ± 2% to 41 ± 4%, $p = 0.003$) functional improvement at 1-year, i.e., NYHA class I or II.
Escher et al. (Escher et al., 2016)	114	Biopsy-proven, virus-negative chronic myocarditis or inflammatory cardiomyopathy	• Prednisone and azathioprine for 6 months	• At short- and long-term follow-up, a significant improvement in LVEF was observed (44.6 ± 17.3% ➔ 51.8 ± 15.5%, $p = 0.006$ and 52.1 ± 15.6%, $p = 0.006$, respectively). • At follow-up, a significant reduction in inflammatory infiltrates was recorded.
Kishimoto et al. (Kishimoto et al., 2014)	41	Chronic HF with LVEF ≤40% or acute HF or arrhythmia and a recent flu-like illness with biopsy-proven myocarditis	• IVIG (1–2 g/kg daily over 2 days) for 15 patients • 26 patients untreated as control arm	• Significant increase in survival for patients treated with IVIG, that was evident starting from day 10. • LVEF improved in all patients (from 17.2 ± 9.0% to 41.4 ± 13.3% in the IVIG group and from 29.8 ± 11.5 to 56.9 ± 17.0% in the control group).
Merken et al. (Merken et al., 2018)	209	Biopsy-proven, virus-negative inflammatory cardiomyopathy	• 53% of patients received SOC + IS (azathioprine and prednisone; cyclosporine only in 11 cases) for at least 6 months	• IS improved the heart transplantation-free survival compared to SOC alone (HR 0.34, 95% CI 0.17 to 0.92) and LVEF after a mean of 12 months follow-up, (+12.2% vs. +7.3%, $p = 0.036$). • First-line therapy (median duration: 19 months) had a success rate of 70%, second-line therapy (median duration: 20 months) had a success rate of 79%, and third-line therapy (median duration: 25 months) had a success rate of 64%.
Caforio et al. (Caforio et al., 2024)	358	Biopsy-proven, virus-negative lymphocytic myocarditis	• 25% of patients were treated with IS on top of SOC, preferably prednisone and azathioprine (1st line) and prednisone and mycophenolate mofetil (2nd and 3rd line)	• ADRs occurred in 13%, 12%, and 0% of cases in the first-, second-, and third-line of treatment, respectively. • No differences in the primary outcome of death or heart transplantation was observed between the two groups (13% in the SOC group vs. 12% in the SOC + IS), however IS patients had a higher rate of relapse.

ADR: adverse drug reaction; CI: confidence interval; CV: cardiovascular; DCM: dilated cardiomyopathy; HF: heart failure; HR: hazard ratio; IS: immunosuppression; IVIG: intravenous immunoglobulin; LVEF: left ventricle ejection fraction; NYHA: New York Heart Association; SOC: standard-of-care; WHF: worsening heart failure.

block. The Study to Evaluate the Efficacy of Immunosuppression in Myocarditis or Inflammatory Cardiomyopathy (IMPROVE-MC; NCT04654988) is currently testing azathioprine plus glucocorticoids in EMB-proven, virus-negative acute myocarditis or inflammatory cardiomyopathy (Ozieranski et al., 2022). Given both immunomodulatory and anti-inflammatory properties, high-dose intravenous immunoglobulins (IVIG) were tested in two clinical trials with inconclusive results (Kishimoto et al., 2014; McNamara et al., 1997).

Small case series have reported promising findings with targeted immunomodulation in subjects with chronic autoimmune myocarditis or inflammatory dilated with rituximab (a chimeric monoclonal antibody targeting CD20) (Tschope et al., 2019) and secukinumab (anti-IL-17] monoclonal antibody) (Frustaci et al., 2023). Conflicting results were provided by small studies reporting on the use of the anti-IL-6 monoclonal antibodies – tocilizumab and sarilumab (Campochiaro et al., 2021; Fa'ak et al., 2023). Monoclonal antibodies targeting interleukin-5 (IL-5), such as mepolizumab and benralizumab, may be beneficial in patients with eosinophilic myocarditis complicating hypereosinophilic syndrome or eosinophilic granulomatosis with polyangiitis (EGPA), but should be adequately evaluated in randomized controlled trials (Belfeki et al., 2021; Bhatt, Jeong, & Neyer, 2024; Colantuono et al., 2020; Goyack et al., 2023; Pink et al., 2023; Trovato, Asada, Fussner, Curtis, & Kahwash, 2024; Wang, Tsai, & Lee, 2023).

The use of NSAIDs can be considered in low-risk patients and in those

with pericardial involvement and preserved LV ejection fraction (LVEF) (Berg et al., 2019; Buiatti et al., 2013; Imazio et al., 2013), while NSAIDs should be avoided in patients with myocarditis complicated by HF (Parish et al., 2023; Writing et al., 2025). Although promising especially in those with pericardial involvement, evidence on the clinical usefulness of colchicine is limited to case reports (Anton-Vazquez, Byrne, Anderson, & Hamzah, 2021; Behbahani-Nejad, Mikolich, Morgenstern, & Mikolich, 2021; Kavgaci, Incedere, Terlemez, & Kula, 2023). A recent retrospective study in patients with acute myocarditis showed that colchicine reduced the risk of 90-day composite outcome (including all-cause death, ventricular arrhythmias, and acute HF) by 34% and this held also true when considering the single components of the composite outcome (Golino et al., 2024). The ongoing CMP-MYTHiC Trial and Registry - CardioMyoPathy With MYocarditis THerapy With Colchicine (CMP-MYTHiC) phase III study is assessing whether colchicine (1 mg daily or 0.5 mg daily if weight $<$ 70 kg) given for 6 months in patients with inflammatory cardiomyopathy associated with ventricular arrhythmias and LVEF would reduce clinical worsening (cardiac death, hospitalization for worsening HF or arrhythmic events, or sustained ventricular tachycardia) or worsening arrhythmic burden (premature ventricular contractions burden increase of 50%, increase in non-sustained ventricular tachycardia NSVT of 30% compared with baseline, or any sustained ventricular tachycardia) (NCT NCT06158698). Anakinra has been successfully used as rescue therapy in small case series of children and adults with acute myocarditis (Cavalli et al., 2016; Malandrino et al., 2024; Maunier et al., 2022; Morini et al., 2026) and to treat complicated multi-inflammatory syndrome in both children (MIS-C) and adults (MIS-A) induced by SARS-CoV-2 infection with concomitant severe myocarditis, with encouraging results (Carter et al., 2020; Della Paolera et al., 2020; La Vecchia et al., 2024; Maunier et al., 2022). The Anakinra versus placebo double-blind Randomized controlled trial for the treatment of Acute MyocarditIS (ARAMIS) was the first and only randomized trial evaluating anakinra in patients with acute myocarditis (Kerneis et al., 2023; Morrow & Verbrugge, 2023). In this trial, 120 young subjects (predominantly males with a mean age of 30 years) with chest pain due to suspected acute myocarditis diagnosed by CMR were randomized to anakinra 100 mg subcutaneously daily or placebo on top of standard of care within 72 h from hospital admission. The majority of patients had an uncomplicated presentation and preserved LVEF. Anakinra was administered for a median of 2 days, and it was safe and well tolerated, yet did not result in a higher number of days free from myocarditis complications, including HF hospitalization, chest pain requiring additional medication, LVEF $<$50%, and ventricular arrhythmias, over a median treatment duration of 2 days. Despite the relatively short treatment period, worsening of chest pain occurred less frequently in patients receiving anakinra (3.5% [anakinra] vs. 10% [placebo]; odds ratio, 0.33; 95% confidence interval, 0.06–1.76). Canakinumab – human anti-IL-1β monoclonal antibody – was effective in a case of fulminant myocarditis associated with adult-onset Still's disease (Ono et al., 2023). Cannabidiol – the non-psychoactive component of marijuana possessing anti-inflammatory and immunomodulatory properties (Lee et al., 2016) – has been tested in the multicenter, double-blind, placebo-controlled Impact of CardiolRx on Myocardial Recovery in Patients With Acute Myocarditis (ARCHER) trial (NCT05180240) (McNamara et al., 2024). Recently presented key findings showed a meaningful structural improvement in the heart due to a reduction in inflammation-driven edema (reduced left ventricular mass and extracellular and intracellular volume) (New Data from the Phase II ARCHER Trial Demonstrate CardiolRx™ Improves Heart Structure in Patients with Acute Myocarditis, Supporting Expansion Across Inflammatory Cardiac Conditions, 2026).

Indication for implantable cardioverter defibrillator (ICD) is a controversial topic based on natural history and resolution of myocarditis. However, wearable implantable cardioverter-defibrillator (ICD) in patients with myocarditis and severe ventricular arrhythmias (ventricular tachycardia or fibrillation) could be used as a bridge to safely observe patients until resolution of the acute episode, if occurs (Caforio et al., 2013).

3.1. *Immune checkpoint inhibitor-associated myocarditis*

Immune checkpoint inhibitor (ICI)-associated myocarditis presents with arrhythmias, HF, or acute coronary syndrome; hence, clinical suspicion is extremely important for early diagnosis (Ammirati & Moslehi, 2023). In most cases, ICI-associated myocarditis occurs soon after the initiation of ICI therapy, usually within 3 months. Increased troponin levels and abnormal electrocardiographic findings (atrial or ventricular extrasystole, non-specific ST segment or T wave changes, life-threatening arrhythmias, complete heart block) are observed (Pradhan, Nautiyal, & Singh, 2019). Echocardiography may show regional wall motion abnormalities or decreased systolic function, although half of the patients have preserved LVEF. Cardiac magnetic resonance imaging may allow tissue characterization (myocardial edema, inflammation, fibrosis) (Mahmood et al., 2018). The gold standard for diagnosis remains EMB, revealing lymphocyte and macrophage infiltration in the myocardium and should be performed whenever feasible since the diagnosis of ICI-associated myocarditis might lead to ICI therapy discontinuation (Mahmood et al., 2018). Of note, ICI-associated myocarditis often occurs alongside other immune-related adverse events such as myositis, myasthenia gravis-like syndrome, pneumonitis, hepatitis, colitis, dermatitis, or endocrinopathy.

Management of ICI-associated myocarditis should involve a multidisciplinary team. Patients should be managed in cardiac intensive care units given the high risk for poor prognosis, especially among those with high levels of troponin, arrhythmias, and hemodynamic instability (Hu et al., 2019). To date, treatment is based on expert opinions. ICI therapy should be suspended for a certain period in case of grade 1 cardiotoxicity (asymptomatic biomarker elevation or imaging abnormality) and permanently for grade $\geq$ 2 (Brahmer et al., 2018). All patients should receive high-dose glucocorticoids (1–2 mg/kg per body weight) and eventually 1 g daily of intravenous methylprednisolone with the addition of mycophenolate mofetil, infliximab, or anti-thymocyte globulin in case an immediate response is not evident (Brahmer et al., 2018). In patients who do not respond to glucocorticoids (in terms of clinical course, abnormal biomarkers, and electrocardiography), the use of alemtuzumab (monoclonal antibody targeting CD52 on B and T cells) (Esfahani et al., 2019), muronomab (monoclonal antibody targeting CD3 on T cells) (Perens, Levi, Alejos, & Wetzel, 2007), abatacept (monoclonal antibody targeting CD152 on activated T cells) (Salem et al., 2019), or infliximab (monoclonal antibody binding tumor necrosis factor) has shown promise but require further investigation (Padegimas et al., 2019; Zhang et al., 2021). However, infliximab is contraindicated in patients with decompensated HF as it might worsen HF course (Geraud et al., 2021).

4. Coronary vasculitides

Systemic vasculitides include large, medium and small vessel vasculitides, where vessel wall damage, endothelial injury, and systemic inflammation are key elements (Clifford & Cohen Tervaert, 2021). Coronary vasculitis may cause coronary stenosis, occlusion, aneurysm, or rupture. Hence, from a clinical standpoint, coronary vasculitis may present with chest pain and/or dyspnea in the setting of acute coronary syndromes, acute de novo congestive HF, arrhythmias, and conduction disturbances, thus suggesting that clinical suspicion is required for appropriate work-up, especially among younger patients (Khanna et al., 2021; Miloslavsky & Unizony, 2014). The increased risk for CV disease in patients with vasculitides is explained both by an excess burden of traditional CV risk factors and systemic inflammation. Importantly, many patients may not have the classical CV risk factors or increased atherosclerosis, but may still exhibit coronary vasomotor dysfunction (Weber et al., 2023).

Coronary vasculitis usually presents as a manifestation of systemic vasculitis, including Kawasaki disease (20% of patients), Takayasu arteritis (10–30% of patients), polyarteritis nodosa (50% of patients), and giant cell arteritis (<1% of patients) (Amano & Suzuki, 1991; Gori, 2021; Khanna et al., 2021). Coronary vasculitis can occur in the anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitides, EGPA (Neumann et al., 2009; Zampieri et al., 2021) and granulomatosis with polyangiitis (Imbalzano et al., 2014). The pathogenesis of these disorders is mainly related to systemic vasculitis and includes autoimmunity and the release of pro-inflammatory cytokines, such as interferon-gamma (IFN-γ), tumor necrosis factor (TNF), and IL-2 (Dye, Kaul, & Clair, 2014). The initial treatment for such disorders remains debated but generally includes high-dose glucocorticoids (usually 1 mg/kg) followed by immunosuppressants as glucocorticoid-sparing agents (Gori, 2021; Khanna et al., 2021) (Fig. 4). However, there is evidence for induction therapy with cyclophosphamide or mycophenolate mofetil and rituximab in ANCA-associated vasculitis with cardiac involvement (Hellmich et al., 2024).

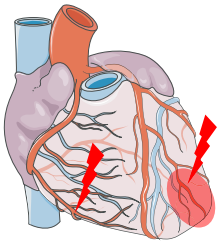
4.1. Kawasaki disease

Kawasaki disease primarily affects children <5 years of age, up to 25% of whom develops coronary vasculitis arteries, with the right and the left anterior descending coronaries being the most frequently involved vessels. If left untreated, complications such as coronary aneurysms occur in a substantial proportion of subjects with Kawasaki disease and coronary involvement (McCrindle et al., 2017). Pathogenesis is poorly understood; however, the currently available evidence points to an exuberant inflammatory response triggered by RNA viruses entering the upper respiratory tract in genetically susceptible children (McCrindle et al., 2017; Rowley et al., 2008; Rowley et al., 2011). Diagnosis relies on clinical suspicion and detailed diagnostic criteria can be found elsewhere (McCrindle et al., 2017).

As soon as a diagnosis is established, IVIG (2 g/kg as a single infusion over 10–12 h) should be administered as first-line treatment, either within 10 days of fever onset or thereafter in the presence of persistently elevated inflammatory markers to reduce the risk of coronary events (Furusho et al., 1984; McCrindle et al., 2017; Newburger et al., 1986) and HF (Moran et al., 2000; Newburger et al., 1989). Concomitant administration of moderate-to-high dose of acetylsalicylic acid (ASA) should be considered until the patient is afebrile (Jone et al., 2024; McCrindle et al., 2017). Glucocorticoid administration for two to three weeks can be considered in subjects with high-risk features (McCrindle et al., 2017). Limited evidence is available for infliximab (Tremoulet et al., 2014) and etanercept (soluble TNF receptor) (Choueiter, Olson, Shen, & Portman, 2010; Portman et al., 2019; Sagiv et al., 2023). These agents, combined with IVIG, have been reported to successfully blunt inflammation but did not reduce IVIG resistance (Choueiter et al., 2010; Portman et al., 2019; Sagiv et al., 2023). In case of IVIG resistance, a second dose of IVIG is recommended, and concomitant high-dose pulse glucocorticoids, infliximab, cyclosporine (calcineurin inhibitor), or anakinra can be considered. Plasma exchange should be reserved to refractory patients failing to respond to the available medical therapies (McCrindle et al., 2017). Low-dose ASA should be administered to patients without evidence of coronary artery changes within 4–6 weeks of acute illness onset to prevent thrombotic occlusion of a coronary artery aneurysm. For patients with rapidly expanding coronary aneurysms, systemic anticoagulation with low-dose ASA is a reasonable option, although available evidence is scarce. Patients with large or giant aneurysms and a recent history of intracoronary thrombosis should be given dual antiplatelet therapy and anticoagulation (McCrindle et al., 2017). In the case of coronary artery thrombosis, thrombolytic therapy should be instituted with low-dose ASA and low-dose heparin or mechanical thrombus removal by cardiac catheterization (McCrindle et al., 2017).

4.2. Takayasu arteritis

Takayasu arteritis (TAK) is a chronic idiopathic granulomatous large-vessel vasculitis affecting the aorta, its main branches, and pulmonary arteries. TAK is more frequently encountered in young women (Joseph, Goel, Thomson, Joseph, & Danda, 2022). When not diagnosed nor treated, TAK may cause stenotic and aneurysmal vascular lesions, potentially leading to stroke, refractory hypertension, HF, and death



Coronary vasculitis

- Stenosis
- Occlusion
- Aneurysm
- Rupture

- **ACS**
- **Acute HF**
- **Arrhythmias**

Kawasaki disease
- IVIG as early as possible + moderate-to-high dose ASA
- Glucocorticoids in high-risk patients
- Low-dose ASA (+ anticoagulation)
- Coronary stenting or bypass only in case of acute myocardial infarction

Takayasu arteritis
- Low-dose glucocorticoids & DMARDs
- Statins
- Antiplatelet/anticoagulant treatment only in case of concurrent CV or cerebrovascular disease
- Invasive therapy only in life- or organ-threatening situations

Polyarteritis nodosa
- Pulse IV/oral high-dose glucocorticoids & cyclophosphamide
- Methotrexate or azathioprine for maintenance
- Invasive therapy after disease activity

Giant cell arteritis
- High-dose glucocorticoids (IV pulse in case of threatened vision loss or orally in absence of manifestations of cranial ischemia)
- Tocilizumab or methotrexate in case of relapse

Behçet's syndrome
- Immunosuppressive therapy (azathioprine or cyclophosphamide) + high-dose glucocorticoids
- Anti-TNF agents (infliximab) in refractory cases
- Anticoagulants in case of intracardiac thrombi

Fig. 4. Overview of the therapeutic management of coronary vasculitis. Coronary vasculitis presents as a manifestation of a systemic vasculitis, the most frequent being Kawasaki disease.
Legend. ASA: acetylsalicylic acid. DMARD: disease-modifying antirheumatic drug. IV: intravenous. IVIG: intravenous immunoglobulin. TNF: tumor necrosis factor.

(Amano & Suzuki, 1991; Joseph et al., 2022). The pathogenesis is still incompletely understood, but is related to impaired immune tolerance and dendritic cell dysfunction, leading to aberrant immune responses following exposure to yet-unknown triggers. Exuberant release of pro-inflammatory cytokines and abundant infiltration of activated T cells into the adventitia and media of large-sized and medium-sized arteries are typically found (Joseph et al., 2022; Tombetti & Mason, 2019). In addition, local release of growth factors contributes to arterial wall edema, extracellular matrix deposition, and myofibroblast proliferation, finally causing arterial stenosis. Arterial dilation may occur through several mechanisms, including increased reactive oxygen species and matrix metalloproteinases that degrade the tunica media and vascular smooth muscle cells (Arnaud, Haroche, Mathian, Gorochov, & Amoura, 2011; Deng et al., 2009). A possible role for B cells is supported by the documentation of anti-aorta and anti-endothelial cell antibodies (Arnaud et al., 2011). In general, two stages are recognized: stage I ("pre-pulseless" phase), characterized by constitutional symptoms (e.g., fatigue, fever, weight loss); stage II ("pulseless" phase), characterized by signs and symptoms caused by the occurrence of acute vascular complications. Only a few patients progress to stage III ("fibrotic" stage), which includes complications caused by chronic arterial damage (Joseph et al., 2022).

Significant advances in the treatment of TAK have been accomplished in the past two decades. First, using low-dose glucocorticoids coupled with disease-modifying anti-rheumatic drugs (DMARDs) results in better disease control, reducing relapses and side effects of glucocorticoid therapy. The latest European League Against Rheumatism (EULAR) guidelines recommend a first treatment phase with a combination of glucocorticoids and conventional synthetic DMARDs (methotrexate, azathioprine, mycophenolate, leflunomide, cyclophosphamide). Glucocorticoids should be administered at 40–60 mg/day prednisone-equivalent for 1 month, then tapered to 15–20 mg/day within 2–3 months, and $\leq$ 10 mg/day after 1 year (Perens et al., 2007). EULAR guidelines suggest a second treatment phase with biologic DMARDs (tocilizumab [IL-6 receptor blocker] (Nakaoka et al., 2013; Pan et al., 2020), infliximab, etanercept, or adalimumab [TNF inhibitors] (Comarmond et al., 2012; Mekinian et al., 2012)) in case of relapse (Hellmich et al., 2020). Similar to EULAR, the American College of Rheumatology endorses combination therapy as first-line treatment but recommends tocilizumab in refractory disease only (Maz et al., 2021). Statin therapy in combination with immunosuppressive treatment has been suggested to significantly reduce relapses independently of cholesterol levels (Kwon et al., 2019). Although antiplatelet therapy is associated with fewer ischemic events in patients with TAK (de Souza et al., 2010), antiplatelet or anticoagulant therapy should not be routinely prescribed unless other indications are present (Hellmich et al., 2020). Current guidelines suggest invasive therapies only in life- or organ-threatening circumstances, refractory hypertension, or when severe functional limitation is present (Maz et al., 2021). Balloon angioplasty is the first-line invasive option of choice, while stenting should be considered after suboptimal angioplasty results, given the higher risk of restenosis, the latter being an important issue with endovascular treatment (Peng et al., 2016). Restenosis occurs less in surgical bypass grafts, so this is the preferred invasive treatment in symptomatic patients despite optimal medical therapy (Huang et al., 2021; Jung et al., 2018). Similarly, aortic aneurysms in TAK are preferably treated with endovascular repair than with open surgery (Joseph et al., 2022).

4.3. Giant cell arteritis

Giant cell arteritis (GCA) is a systemic vasculitis of medium and large arteries, predominantly affecting the aortic branches of the head and neck. GCA often presents in combination with polymyalgia rheumatica, headache, and constitutional symptoms (Kushnir, Restaino, & Yuzefpolskaya, 2016). Involvement of coronary arteries is relatively infrequent (Armellin et al., 2017; Mednick, Farmer, Khan, Warder, & Ten Hove, 2016). Aortic insufficiency due to aortic aneurysm, as well as myocarditis and pericarditis, can also occur in patients with GCA (Miloslavsky & Unizony, 2014). While the cardiovascular pathogenesis of GCA is still poorly defined, genetic predisposition and concomitant exposure to certain environmental factors (e.g., infections, smoking) play an important role (Pugh et al., 2022). Timely detection and adequate management of CV involvement in subjects with active GCA is of utmost importance as it may lead, among others, to ischemic events and organ damage, including vision loss (Hellmich et al., 2020). Similar to TAK, therapeutic management includes high-dose glucocorticoid therapy to taper once the disease is controlled, aiming at a target dose of 15–20 mg daily within 2–3 months and to $\leq$5 mg daily after 1 year. Tocilizumab should be considered in case of poor clinical response or relapse (Hellmich et al., 2020; Stone et al., 2017).

4.4. Polyarteritis nodosa

Polyarteritis nodosa (PAN) is a rare systemic necrotizing vasculitis affecting the medium-sized arteries in middle-aged and older adults (Chung et al., 2021). Besides idiopathic PAN, secondary forms can occur in hairy cell leukemia or hepatitis B. Clinical features can vary depending on arteries and organs involved, with the kidneys, skin, joints, muscles, nerves, and mesentery being the most frequently affected (Dye et al., 2014).

Cardiac involvement is found in nearly 25% of patients with PAN, and up to 50–60% upon autopsy, mainly consisting of coronary vasculitis (Chimenti et al., 2020; Holsinger, Osmundson, & Edwards, 1962; Schrader, Hochman, & Bulkley, 1985; Zimba & Bagriy, 2017). Coronary arteries present with diffuse luminal narrowing, aneurysms, distal pruning and dissection, which can often be observed on CMR imaging (Dye et al., 2014; Peters et al., 2018). An increased inflammatory burden occurring in these patients may also account for accelerated atherosclerosis and microvascular dysfunction, further contributing to coronary artery disease and HF (Chimenti et al., 2020; Cohen Tervaert, 2013; Peters et al., 2018; Solis-Jimenez et al., 2022).

In patients with severe active PAN, initial treatment includes pulse intravenous glucocorticoids or oral high-dose glucocorticoids combined with cyclophosphamide (or azathioprine or methotrexate if cyclophosphamide is not tolerated). Azathioprine or methotrexate and glucocorticoids are indicated in subjects with non-severe forms of active PAN (Chung et al., 2021). Methotrexate or azathioprine are recommended over cyclophosphamide for remission maintenance (Chung et al., 2021). However, this is unlikely to revert aneurysms that, if untreated, may complicate with thrombosis, embolism, rupture, and fistulae formation (Dye et al., 2014). Before catheter-based or open surgical interventions for the repair of coronary aneurysms, pharmacological control of vascular inflammation is warranted. In order to reduce the risk of peri-procedural complications, invasive therapy should be postponed until disease activity is well controlled by immunosuppressive therapy and patients should be managed in multidisciplinary teams at specialized centers (Hellmich et al., 2020).

4.5. Behçet's syndrome

Behçet's syndrome (BS) is a systemic vasculitis characterized by mucocutaneous and ocular manifestations with variable involvement of many organ systems. Recurrent oral and genital ulcers are often the first manifestation of BS, with a prevalence of up to 95% in both male and female patients, but clinical subsets are heterogeneous and may include several systemic presentations represented by skin lesions, articular, gastrointestinal, neurological involvement, and cardiovascular (CV) disease (Emmi, Bettiol, Hatemi, & Prisco, 2024). Among different phenotypes, CV involvement is one of the major causes of morbidity and mortality in BS patients and venous thrombosis, both deep and superficial, represents the most frequent CV manifestation (up to 40% of patients in different epidemiological studies) (Saadoun, Bodaghi, &

Cacoub, 2024). Vascular involvement could affect almost every vessel, although veins are more commonly involved than arteries, with a significant thrombotic tendency that appears to be unassociated with traditional thrombophilic factors. Cardiac involvement, although rare, can be a life-threatening complication of BS, especially in cases of delayed diagnosis and can occur as coronary artery disease (i.e., coronary aneurysms and stenotic lesions), intracardiac thrombosis and valvular dysfunction (Emmungil et al., 2014). Pericarditis, myocarditis, and aneurysms of aorta or its branches occur less commonly (Demirelli, Degirmenci, Inci, & Arisoy, 2015).

Despite the apparent complexity of the pathogenesis of BS, important components incude the genetic background (HLA-B*51 and variants in the genes encoding important inflammasome components such as A20 but these are not yet fully understood), innate and adaptive immune activation by multiple pathogens and the consequent interaction of T lymphocytes (with a Th1 and Th17 phenotype) with activated neutrophils (the main responsible agents for tissue damage), which seem to have an intrinsic hyperactivation in BS patients (Emmi et al., 2014).

The treatment of BS differs according to the involved system and relies on different drugs. Immunosuppressants represent the cornerstone of treatment for venous and arterial events, while the role of anticoagulants remains a matter of debate (Yazici, Seyahi, Hatemi, & Yazici, 2018). High-dose glucocorticoids are combined with traditional or biological DMARDs for moderate-to-severe involvement. In patients with refractory venous thrombosis, TNF inhibitors, with or without traditional DMARDs, are the main treatment, also combined with anticoagulants. Anticoagulants and immunosuppressants (preferably cyclophosphamide or anti-TNF) should be used together in patients with intracardiac thrombi or cerebral venous sinus thrombosis, as well as in cases of severe thrombosis of larger veins (especially the vena cava) (Emmi et al., 2024).

5. Non-infective endocarditis

Non-infective endocarditis, also known as non-bacterial thrombotic endocarditis (NBTE) or Libman-Sacks endocarditis, is a rare condition characterized by sterile endocardial vegetations composed of fibrin and platelet clumps with or without detectable bacteriemia (Deppisch & Fayemi, 1976; Gross, 1940; Hurrell, Roberts-Thomson, & Prendergast, 2020; Libman, 1924). If left untreated, this condition is associated with substantial morbidity (e.g., valve dysfunction, HF) and high mortality rates (Zmaili, Alzubi, Lo Presti Vega, Ababneh, & Xu, 2022). It involves female subjects in around 70% of cases between the fourth and eighth decades of life (Ahmed et al., 2025). NBTE is associated with active cancers (34% to 46% of patients), especially pancreatic, lung, breast, and ovarian cancers and myeloproliferative disorders (Bussani et al., 2019; Venepally et al., 2022), and autoimmune or rheumatic disorders (20% to 40% of patients) like SLE, RA, and antiphospholipid syndrome, burns (El-Shami, Griffiths, & Streiff, 2007; Ferrans & Rodriguez, 1985; Galve et al., 1988; Gonzalez Quintela, Candela, Vidal, Roman, & Aramburo, 1991; Zmaili et al., 2022), or coronavirus disease 2019 (COVID-19) (Ahmad et al., 2023; Chan et al., 2021). In particular, burns, sepsis, and indwelling catheters could predispose to a hypercoagulable state and were reported to cause NBTE (Ahmed et al., 2025). Diagnosis is primarily clinical, with systemic embolism (especially to the spleen, kidney, retina, brain or digits) as the main clinical sign, although most patients are asymptomatic. Blood cultures, urinalysis, laboratory tests (complete blood count, coagulation and autoimmunity panel, inflammatory biomarkers), and non-invasive multimodality imaging (transesophageal echocardiography, cardiac computed tomography and, eventually, CMR and positron emission tomography) should be considered to diagnose NBTE (Hurrell et al., 2020; Liu & Frishman, 2016). Key pathogenic mechanisms implicated in NBTE include immune dysfunction with endothelial activation and platelet aggregation leading to thrombus formation on cardiac valve leaflets, especially on the left side (Bussani et al., 2019). Pro-inflammatory cytokines, hypoxia, and turbulent blood flow can induce endothelial activation and injury, priming the environment for platelet aggregation and fibrin deposition (Bazzan, Vaccarino, & Marletto, 2015; Nakanishi et al., 1998; Reverter et al., 1996; Truskinovsky & Hutchins, 2001).

Management should focus on identifying and treating possible underlying conditions, either autoimmune, rheumatologic or malignant. Palliative care is reserved to cases of advanced malignancy associated with NBTE (El-Shami et al., 2007). Surgery is rarely indicated and might be considered in cases of hemodynamic instability, refractory HF, recurrent embolic events while on anticoagulation, large vegetations, and prosthetic valve involvement (Asopa, Patel, Khan, Sharma, & Ohri, 2007; Hurrell et al., 2020; Kaneyuki et al., 2017). Since vegetations tend to be more friable than in infective endocarditis, to reduce the risk of systemic embolism, all patients diagnosed with NBTE receive anticoagulant therapy unless contraindicated, with low-molecular-weight and unfractionated heparin being preferred over warfarin, whereas insufficient evidence currently supports the use of direct oral anticoagulants (Cohen et al., 2015; Delgado et al., 2023; Petrescu et al., 2018; Whitlock, Sun, Fremes, Rubens, & Teoh, 2012).

6. Cardiac sarcoidosis

Cardiac involvement in sarcoidosis can occur in up to 25% of cases (Myadam et al., 2023; Rosenfeld et al., 2021; Takaya, Nakamura, Nishii, & Ito, 2021). Pathogenesis relies on dysregulated innate and adaptive immunity synergistically contributing to the formation of non-caseating cardiac granulomas. Over time, granulomas can lead to fibrosis and disrupt cardiac function (HF) or the conduction system (brady-, tachyarrhythmias, and sudden cardiac death). IFN-γ and TNF, primarily secreted by T-helper 1 cells, play a role in recruiting and activating macrophages, which are involved in the formation and development of granulomas (Hamzeh, Steckman, Sauer, & Judson, 2015; Rosenfeld et al., 2021). Increased expression of the NLRP3 inflammasome was also observed in granulomas from patients with clinically active cardiac sarcoidosis, together with evidence of active inflammation upon cardiac imaging (Kron et al., 2019).

Evidence regarding the optimal therapeutic management of cardiac sarcoidosis is limited to date. Glucocorticoids represent the mainstay of therapy, although their effectiveness in preventing arrhythmic outcomes appears to be poor (Mankad, Mitchell, Birnie, & Kron, 2019). A recent systematic review of the available literature suggests that glucocorticoids and immunosuppressants might aid in preserving atrioventricular conduction and LV systolic function (Fazelpour et al., 2021). Methotrexate, azathioprine, mycophenolate mofetil, or TNF antagonists (e.g., infliximab or adalimumab) are often used to spare glucocorticoids as second-line therapies. No solid evidence supporting one drug over another is currently available. These drugs might also be considered in patients refractory to glucocorticoids, however, cautious use is recommended given the risk for side effects such as serious infection, hematologic cancer and increased risk of HF-related death (Rosenthal et al., 2019).

The Multimodality assessment of granulomas in cardiac sarcoidosis: Anakinra Randomized Trial (MAGiC- ART; NCT04017936) evaluated IL-1 blockade with anakinra in patients with cardiac sarcoidosis (Kron et al., 2021), showing that adding anakinra to standard-of-care significantly reduces high-sensitivity CRP at day 28 and appears safe overall (Kron et al., 2023). The Cardiac Sarcoidosis Multi-Center Randomized Controlled Trial (CHASM-CS-RCT; NCT03593759) is testing whether a combination of low-dose prednisone and methotrexate decreases cardiac inflammation (measured by ^{18}F-fluorodeoxyglucose positron emission tomography [FDG-PET] at 6 months) and improve quality of life as compared with high-dose prednisone (Birnie et al., 2020). The Japanese Antibacterial Drug Management for Cardiac Sarcoidosis (J-ACNES; UMIN000025936) is currently evaluating whether the addition of antibiotic therapy (clarithromycin and doxycycline) to glucocorticoids mitigates cardiac inflammation at 6 months, as assessed by

reduced standardized uptake value on FDG-PET (Ishibashi et al., 2018). The trial is based on the evidence suggesting *Propionibacterium acnes* as a potential trigger for sarcoidosis, with its DNA and antigens often found in sarcoid lesions, particularly in Japanese populations.

Ongoing clinical trials enrolling patients with cardiac sarcoidosis are summarized in Table 3.

7. Systemic sclerosis

Systemic sclerosis (SSc), also known as scleroderma, is a rare immune-mediated disease characterized by fibrosis of the skin and internal organs and vasculopathy (Denton & Khanna, 2017). The pathogenesis is complex and poorly understood. Scleroderma can be divided into 2 forms – localized scleroderma (limited to the skin only and including morphea and linear scleroderma) and systemic sclerosis (including limited systemic sclerosis and diffuse systemic sclerosis). Limited systemic sclerosis was formerly known as calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia (CREST) syndrome, characterized by systemic manifestations and internal organ involvement, leading to increased mortality.

Cardiac involvement is a common feature in SSc and affects the myocardium, pericardium and conduction system (Jones, Bottini, Boin, & Marban, 2025). Pulmonary arterial hypertension is also well recognized and the leading cause of death from SSc, and it may be primary or secondary due to interstitial lung disease. Cardiac involvement in SSc is clinically overt in up to 30% of patients but the advent CMR has revealed that there is subclinical disease in over 70% of patients (Dumitru et al., 2021). Primary cardiac involvement can occur in both limited and diffuse SSc. The highest risk of cardiac involvement is in those with rapidly progressing skin disease, skeletal myopathies and the presence of the U3-RNP antibody (Dumitru et al., 2021). Primary cardiac involvement is characterized by myocardial microvascular disease causing impaired coronary flow reserve, and diffuse and focal myocardial fibrosis (Denton & Khanna, 2017). Treatment of SSc is limited by poor pathophysiological understanding of the disorder and limited randomized controlled clinical trials. Many manifestations are treated individually, for example the symptomatic treatment of esophageal dysmotility or Raynaud's phenomenon. There is no known immunosuppressive treatment that augments the disease course or cures the disease. Cyclophosphamide and mycophenolate mofetil are used for cardiac, lung, and skin disease; methotrexate for skin, inflammatory arthritis, and myositis; azathioprine for skin, lung disease, and myositis; and hydroxychloroquine for skin disease (Denton & Khanna, 2017). Caution with high-dose glucocorticoids must be taken in these patients due to the risk of steroid-induced scleroderma renal crisis.

8. Other inflammatory disorders involving the heart

MIS is a rare, severe postinfectious syndrome first described in children as a Kawasaki-like syndrome following COVID-19 and later recognized also in adults, which is characterized by multiorgan involvement (La Vecchia et al., 2024). Clinically, patients with MIS-A may present with persistent fever, gastrointestinal symptoms, mucocutaneous inflammation, hematological and coagulation disorders, and increased levels of inflammatory biomarkers (CRP, IL-6, and ferritin) (La Vecchia et al., 2024). The cardiovascular system is frequently involved in MIS-A, including arrhythmias, myocarditis, pericarditis, pericardial effusion, and coronary aneurysms (Patel et al., 2021). Despite the young age, these patients could be at high risk of severe complications, such as cardiogenic shock, needing intensive care unit admission (Feldstein et al., 2021). Notably, compared with children, adults experience a higher incidence of thrombosis, death, and severity when the heart is involved (Patel et al., 2021). The pathophysiology of MIS is still a matter of investigation and is exhaustively summarized elsewhere (La Vecchia et al., 2024).

Due to the lack of randomized trials, expert consensus suggests to start immunosuppressive or immunomodulation treatment (including glucocorticoids, IVIG, or cytokine-targeted therapy) as soon as possible to slow disease progression and avoid hemodynamic instability (Hekimian et al., 2021; Vogel et al., 2021). Intravenous glucocorticoids should be initiated once alternative diagnoses are excluded. Similarly to myocarditis, low-dose glucocorticoids could be used for low-to-moderate-risk disease, while high doses are needed in patients presenting with cardiogenic shock (Ammirati et al., 2020; Hekimian et al., 2021). IVIG (2 g/kg in 1 or 4 divided infusions every 6 h) should be considered as a first-line therapy in patients with cardiac dysfunction within the first ten days from disease onset and can be administered together with low-to-moderate glucocorticoids in patients with high-risk

Table 3
Clinical trials testing treatments for cardiac sarcoidosis.

Authors, reference	Number of patients	Inclusion criteria	Treatment	Study objectives
CHASM-CS-RCT (NCT03593759) (Birnie et al., 2020)	194	Active, clinically manifest CS with advanced conduction system disease, significant sinus node dysfunction, ventricular arrhythmias, LV or RV dysfunction	• Prednisone 0.5 mg/kg/day for 6 months (maximum dose 30 mg daily) or prednisone 20 mg daily for 1 month, then 10 mg daily for 1 month, then 5 mg daily for one month then stop and • methotrexate 15–20 mg once weekly for 6 months	Primary endpoint: summed perfusion rest score on 6-month PET as a measure of myocardial fibrosis/scar.
MAGiC-ART (NCT04017936) (Kron et al., 2021)	28	CS with cardiac uptake on FDG-PET within 2 months and hs-CRP $\geq$ 2 mg/L	• Anakinra 100 mg daily + SOC for 28 days • SOC alone	Primary endpoints: • number of subjects enrolled, stratified by race/ethnicity (feasibility endpoint); • change in hs-CRP and IL-6 after 4 weeks of treatment (efficacy endpoint).
J-ACNES (UMIN000025936) (Ishibashi et al., 2018)	80	CS needing de novo glucocorticoid therapy with abnormal cardiac uptake on FDG-PET	• Prednisolone 30 mg daily for 1 month, then tapered over 2 to 4 weeks, with a maintenance dose of 7.5 mg daily + clarithromycin 400 mg daily for 24 weeks + doxycycline 100 mg daily for 22 weeks after 2 months of clarithromycin • Prednisolone 30 mg daily for 1 month, then tapered over 2 to 4 weeks, with a maintenance dose of 7.5 mg daily	Primary endpoint: change in total SUV on FDG-PET at 6 months.

hs-CRP: high-sensitivity C-reactive protein; CS: cardiac sarcoidosis; FDG-PET: fluoro-D-glucose positron-emission tomography/computed tomography; IL-6: interleukin-6; LV: left ventricle; PET: positron-emission tomography; RV: right ventricle; SOC: standard-of-care; SUV: standardized uptake value.

disease (Hekimian et al., 2021). Anakinra (100 mg daily subcutaneously or intravenously at a dose of 10 mg/kg daily in case of severe hyperinflammation) was used with glucocorticoids and in glucocorticoid-dependent severe cases with positive outcomes (Rinaldi, Tomelleri, Campochiaro, & Dagna, 2023; Vogel et al., 2021). In case of poor response to anakinra, tocilizumab (recombinant IL-6 receptor antagonist) provided encouraging results in some case reports (Morris et al., 2020; Patel et al., 2021; Vogel et al., 2021). Finally, thromboprophylaxis should always be prescribed especially for hospitalized patients and those with high-risk features (Bonaventura et al., 2021; Connors & Levy, 2020). However, no consensus exists on the duration of such treatment that a balance between thrombotic and hemorrhagic risk and resolution of the hyperinflammatory state by means of inflammatory markers should be considered.

Other hyperinflammatory disorders sharing clinical features with MIS are adult-onset Still's disease (AOSD) and macrophage activation syndrome (MAS). AOSD presents in young adults with spiking fever and a concurrent salmon-colored skin rash on the trunk and the extremities, elevated levels of inflammatory biomarkers (CRP, erythrocyte sedimentation rate, IL-6, ferritin), arthritis, pharyngitis, and lymphadenopathy. However, cardiac involvement with pericarditis, myocarditis, or cardiac dysfunction is rare (Giacomelli, Ruscitti, & Shoenfeld, 2018). AOSD may complicate with MAS, that presents with fever, lymphadenopathy, hepatosplenomegaly, encephalopathy, disseminated intravascular coagulation, and increased levels of ferritin and liver injury enzymes (Giacomelli et al., 2018; Hines et al., 2022). Glucocorticoids are first-line therapy for AOSD started at a dosage of 0.5–1 mg/kg/day, that provides a rapid response and fewer relapses, followed by tapering. However, glucocorticoid dependence is reported in up to 45% of patients (Giacomelli et al., 2018). Intravenous high-dose glucocorticoids should be considered in case of visceral involvement and/or MAS development (Govoni, Bortoluzzi, Rossi, & Modena, 2017). Methotrexate is the most commonly prescribed DMARD as a glucocorticoid-sparing agent. In case of poor response, other synthetic DMARDs may be considered, although few data are available for hydroxychloroquine, IVIG and cyclosporine. The recent consensus for the diagnosis and management of children and adults with Still's disease suggests that early initiation of therapy with IL-1 or IL-6 inhibitors may also decrease the number of patients with a chronic persistent course, with very favorable short-term outcomes and markedly limited glucocorticoid treatment side-effects (Fautrel et al., 2024).

9. Conclusion

Inflammatory heart diseases are typically caused by dysregulated immunity with aberrant inflammatory responses following a plethora of infectious or non-infectious noxae. The pericardium (pericarditis) and the myocardium (myocarditis) are most frequently involved. The etiology is considered idiopathic in many patients. In secondary forms, infection, cancer, systemic autoimmune, rheumatic or autoinflammatory disorders, and toxic agents or irritants are often present. The precise immune dysregulation and disease-specific molecular signaling are still poorly understood in many inflammatory heart diseases. Such lack of mechanistic understanding often translates into non-specific, non-selective therapeutic approaches primarily employing glucocorticoids, which carry significant safety concerns, especially when high doses or long-term use become necessary. Over the recent years, targeted therapeutic strategies have been developed and successfully evaluated in clinical trials of selected inflammatory heart diseases. Currently, targeted therapies with selective IL-1 inhibitors are only approved for the management of recurrent/refractory pericarditis. Additional research is urgently warranted to improve the current understanding of the pathobiology of inflammatory heart diseases, to identify novel molecular targets for intervention, and to develop and adequately validate targeted therapeutic strategies for a growing number of inflammatory heart diseases.

CRediT authorship contribution statement

Aldo Bonaventura: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Data curation, Conceptualization. **Marco Giuseppe Del Buono:** Writing – review & editing, Writing – original draft, Investigation. **Michele Golino:** Writing – review & editing, Writing – original draft, Investigation. **Nicola Potere:** Writing – review & editing, Writing – original draft, Investigation. **Alessandra Vecchié:** Writing – review & editing, Writing – original draft, Investigation. **Danilo Malandrino:** Writing – review & editing, Writing – original draft, Investigation. **Benjamin Van Tassell:** Writing – review & editing, Supervision. **Taryn Youngstein:** Writing – review & editing, Writing – original draft, Supervision, Investigation. **Brittany N. Weber:** Writing – review & editing, Writing – original draft, Supervision, Investigation. **Antonio Abbate:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Investigation, Conceptualization.

Declaration of competing interest

AA has served as a consultant for Kiniksa, Novo Nordisk, and Monte Rosa Therapeutics. BNW has served as a consultant for Kiniksa, Novo Nordisk, BMS, and Oruka. The other authors have nothing to disclose.

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Data availability

No data was used for the research described in the article.

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