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PERICARDIAL DISEASE (AL KLEIN AND CL JELLIS, SECTION EDITORS)

Pediatric Pericarditis: Update

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Abstract

Purpose of Review While there have now been a variety of large reviews on adult pericarditis, this detailed review specifically focuses on the epidemiology, clinical presentation, diagnosis, and management of pediatric pericarditis. We have tried to highlight most pediatric studies conducted on this topic, with special inclusion of important adult studies that have shaped our understanding of and management for acute and recurrent pericarditis.

Recent Findings We find that the etiology of pediatric pericarditis differs from adult patients with pericarditis and has evolved over the years. Also, with the current COVID-19 pandemic, it is important for pediatric clinicians to be aware of pericardial involvement both due to the infection and from vaccination. Oftentimes, pericarditis maybe the only cardiac involvement in children with COVID-19, and so caregivers should maintain a high index of suspicion when they encounter children with pericarditis.

Summary Large-scale contemporary epidemiological data regarding incidence and prevalence of both acute and recurrent pericarditis is lacking in pediatrics, and future studies should focus on highlighting this important research gap. Most of the current management strategies for pediatric pericarditis are from experiences gathered from adult data. Pediatric multicenter trials are warranted to understand the best management strategy for those with acute and recurrent pericarditis.

Case Vignette A 6-year-old child with a past history of pericarditis almost 2 months ago comes in with a 2-day history of chest pain and fever. Per mother, he stopped his steroids about 2 weeks ago, and for the last 2 days has had a temperature of 102F and has been complaining of sharp mid-sternal chest pain that gets worse when he lies down and is relieved when he sits up and leans forward. On examination, he is tachycardic (heart rate 160 bpm), with normal blood pressure for age. He appears to be in pain (5/10), and on auscultation has a pericardial friction rub. His lab studies are notable for elevated white blood cell count and inflammatory markers (CRP and ESR). His electrocardiogram reveals sinus tachycardia and diffuse ST-elevation in all precordial leads. His echocardiogram demonstrates normal biventricular function and a trace pericardial effusion. His cardiac MRI confirms recurrent pericarditis. He is started on indomethacin and colchicine. He has complete resolution of his symptoms by day 3 of admission and is discharged with close follow-up.

Keywords Pediatric · Pericardial disease · Pericarditis · Children

This article is part of the Topical Collection on *Pericardial Disease*

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Introduction

The pericardium (from the Greek p1ri´, "around" and ka´rdion, "heart") is a double-layered sac (with a serous visceral layer and a fibrous parietal layer) enclosing the heart and the roots of the great vessels. The "pericardial cavity" is the space between these layers that contains pericardial fluid, which facilitates smooth movement of the heart throughout the cardiac cycle [1••]. Pericarditis is one of the most common pericardial diseases characterized by inflammation of the pericardial layers [1••] (Fig. 1).

Etiology (Table 1)

Acute Pericarditis

The underlying etiology typically depends on patient factors along with the geographical location. Classically, causes are divided into infectious vs. non-infectious etiologies (Table 1) [2 –6]. The most common identifiable etiology is viral in origin in developed countries [7, 8], whereas in the developing world, tuberculosis (TB) is the most frequent etiology [6, 9]. In the majority of cases, the underlying etiology cannot be identified and such cases are termed "idiopathic" [10, 11•, 12]. In children, there has been a changing trend in the underlying etiology of pericarditis, with post-cardiotomy pericardial inflammation becoming a more common etiology while infectious etiologies becoming less frequent [13, 14•, 15•]. In a large database study of hospitalized pediatric patients with pericarditis and pericardial effusions, post-cardiac surgery (54%), neoplasia (13%), and renal disease (13%) were more frequent, while idiopathic or viral pericarditis (5%) and rheumatologic (5%) causes were less likely underlying etiologies [14•].

Recurrent Pericarditis

The etiology of recurrent pericarditis remains poorly understood, with multiple theories proposed. In a subset of cases, a viral etiology may be uncovered. However, frequently no specific etiology is found, leading to a diagnosis of idiopathic recurrent pericarditis (IRP) [16]. A growing body of literature indicates that these episodes labeled as idiopathic are due to an immune-mediated phenomena including both autoimmune and autoinflammatory processes [17, 18] with the body's immune system reacting to self-antigens (exposed due to damage during the primary acute pericarditis episode) or exogenous antigens (viral- or bacterial-derived molecules) [17]. This theory is further supported by the occurrence of recurrent pericarditis in autoimmune conditions (systemic lupus erythematosus, juvenile rheumatoid arthritis), elevated anti-nuclear antibody levels in patients with IRP compared to controls [17, 19–21], and similarity to other hereditary autoinflammatory disorders (such as periodic fever syndrome) [19] which are characterized by primary dysfunction of the innate immune system with good

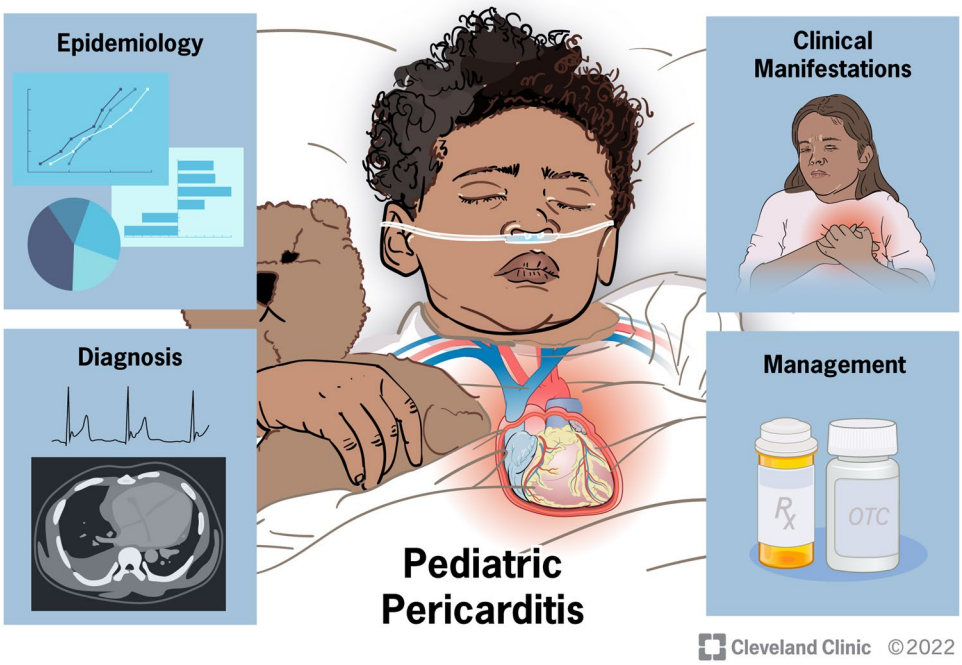

Fig. 1 This figure demonstrates topics discussed in the current review on pediatric pericarditis which focuses on epidemiology, clinical manifestations, diagnosis, and management. (Reprinted with permission, Cleveland Clinic Foundation© 2022. All Rights Reserved.)

Table 1 Etiologies of pericarditis

A. Idiopathic (presumed to be viral, post viral, or immune mediated)

In most cases, majority of patients are not found to have an identifiable cause. Frequently such cases are presumed to have a viral or autoimmune etiology.

B. Infectious causes:

❖ **Viral (common):** enteroviruses (coxsackievirus, echoviruses), coronavirus, influenza, herpesviruses (EBV, CMV, HHV-6), adenoviruses, varicella, mumps, rubella, parvovirus B19, hepatitis B and hepatitis C viruses, HIV

❖ **Bacterial:** *Mycobacterium tuberculosis* (common, other bacterial rare), *Coxiella burnetii*, *Borrelia burgdorferi*, rarely: *Pneumococcus* spp., *Meningococcus* spp., *Gonococcus* spp., *Streptococcus* spp., *Staphylococcus* spp., *Haemophilus* spp., *Chlamydia* spp., *Mycoplasma* spp., *Legionella* spp., *Leptospira* spp., *Listeria* spp., *Providencia stuartii*

❖ **Fungal (very rare):** *Aspergillus* spp., *Blastomyces* spp., *Candida* spp. (more likely in immunocompromised host), *Histoplasma* spp. (more likely in immunocompetent patients)

❖ **Parasitic (very rare):** *Toxoplasma* spp., *Echinococcus* spp., *Trypanosoma cruzi*

C. Non-infectious causes:

❖ **Autoimmune (common):**
- ■ Systemic inflammatory diseases: SLE, rheumatoid arthritis, scleroderma, Sjögren syndrome, vasculitis, mixed connective disease
- ■ **Autoinflammatory diseases**: especially familial Mediterranean fever and tumor necrosis factor-associated periodic syndrome (TRAPS), IgG4-related disease
- ■ **Post-cardiac injury syndromes**: immune-mediated after cardiac trauma in predisposed individuals
- ■ **Other:** granulomatosis with polyangiitis (Wegener), allergic granulomatosis (Churg-Strauss syndrome), polyarteritis nodosa, sarcoidosis, inflammatory bowel disease (Crohn, ulcerative colitis), Whipple, giant cell arteritis, Behçet syndrome, rheumatic fever

❖ **Neoplastic:**
- ■ **Primary tumors:** rare, most commonly pericardial mesothelioma
- ■ **Secondary metastatic tumors:** common, most commonly lung and breast cancer, lymphoma

❖ **Metabolic**
- ■ Uremia, myxedema, anorexia nervosa

❖ Trauma
- ■ **Early onset (rare):**
  - Direct: penetrating trauma, esophageal injury
  - Indirect injury (non-penetrating thoracic injury)
- ■ **Delayed onset:**
  - Post-cardiac injury syndromes (e.g., post-myocardial infarction, post-pericardiotomy, and post-percutaneous intervention)

❖ **Iatrogenic:** coronary percutaneous intervention, pacemaker lead insertion, and radiofrequency ablation

❖ **Drug and toxin related**
- ■ **Drug-induced lupus erythematosus reaction**
  - Procainamide, hydralazine, isoniazid, methyldopa, mesalazine
- ■ **Hypersensitivity reaction**
  - Penicillins, tryptophan, cromolyn sodium
- ■ **Idiosyncratic reaction**
  - Minoxidil, methysergide, cyclosporine, cyclophosphamide, sulfa drugs
- ■ **Pericarditis frequently associated with cardiomyopathy**
  - Anthracyclines
- ■ **Venoms**
  - Scorpion-fish stings
- ■ **Serum sickness reactions**
  - Foreign antisera, blood products
- ■ **Direct contact**
  - Talc, tetracyclines, asbestos, iron

❖ **Radiation**
- ■ **Early onset**
- ■ **Late onset** (up to 15–20 years following exposure)

Other (common): amyloidosis, aortic dissection, pulmonary arterial hypertension, and chronic heart failure

Other (uncommon): congenital partial and complete absence of the pericardium

From Adler Y, et al. Eur Heart J. 2015;36(42):2921–64, by permission of Oxford University Press) [1••]

response to corticosteroids [22]. Female sex, previous corticosteroid use, and frequent prior recurrences are risk factors for future recurrence [23–25].

In a multicenter cohort study, recurrences in children and adolescents were idiopathic or viral in 89.1% of cases, followed by post-cardiotomy syndrome (9.1%) and familial

Mediterranean fever (0.9%) [26••]. Risk factors for recurrent pericarditis in children were noted to be erythrocyte sedimentation rate ≥ 50 mm/h, absence of myocarditis, C-reactive protein ≥ 125 mg/L, non-idiopathic etiology, and corticosteroid treatment compared to non-steroidal anti-inflammatory therapy [27–30].

Pericarditis Due to COVID-19 Infection and COVID-19 Vaccination

Of recent interest, the cardiovascular ramifications of SARS-CoV-2 have now been widely established, including pericarditis, myocarditis, and conduction abnormalities [31, 32]. The majority of cases of pericardial involvement have been associated myocardial involvement with associated troponin elevation.

The exact incidence of pericarditis in COVID-19 patients is currently unknown, but post-mortem studies have identified pericarditis in approximately 20% of confirmed cases [33]. The precise pathophysiological mechanism of pericardial involvement in patients with COVID-19 remains to be completely elucidated. Prevailing hypotheses at present propose a hyperinflammatory and hyperimmune reaction induced by SARS-CoV-2 rather than direct infection of the pericardium and myocardium [34, 35]. Studies evaluating pericardial disease among children with COVID-19 remain limited to small case reports. Of those, acute pericarditis and pericardial effusion with tamponade [36] in children with COVID-19 have been described, even in the absence of the typical concomitant respiratory findings, underscoring the importance of maintaining a high index of suspicion during the pandemic [37•].

Standard diagnostic testing for pericarditis, in the form of ECG, echocardiography, and chest radiography, can be used to identify suspected cases of pericardial involvement with COVID-19. Cardiac MR and CT may also be of diagnostic aid [38].

Despite initial concern regarding the use of NSAIDs in the setting of a COVID-19 infection, current guidelines per the World Health Organization and Food and Drug Administration have not acknowledged any link between NSAIDs and worsening COVID-19 symptoms or outcomes [39 , 40], and recent studies do not support restricting the use of NSAIDs [41–43]. In the absence of robust evidence on the management of COVID-19-associated pericarditis, standard treatments for pericarditis, including NSAIDs, corticosteroids, colchicine, and anakinra, have been used safely in the setting of SARS-COV2 infection [34, 44]. Most cases of acute pericarditis associated with COVID-19 in the literature have been reported to be treated with colchicine and NSAIDs [34].

Data evaluating the incidence of pericarditis and cardiac complications related to COVID-19 vaccines in particular continue to emerge [45••, 46••, 47••]. While some studies have demonstrated an increased incidence of myocarditis and myopericarditis, particularly among young males (< 40 years), after the second dose of the mRNA vaccine, and within 7 days after mRNA COVID-19 vaccination [45••, 46••, 47••], others have not [46••, 48]. In the largest study to date evaluating acute cardiac outcomes following COVID-19 vaccination or infection, no association between the adenovirus-based COVID-19 vaccine or the mRNA-based vaccines and pericarditis was found [46••]. A recent analysis of 46 studies conducted by Pillay et al. [35] found that, among individuals aged 12–17, 18–29, or 18–39 years, the administration of an mRNA vaccine for COVID-19 ≥ 31 days apart could lower the incidence of myocarditis or pericarditis. Balancing the evolving data and the rare adverse reactions to vaccination, with the known risks of COVID-19 illness, current CDC guidance continues to recommend that all individuals 6 months and older receive for the mRNA COVID-19 vaccine [49].

Epidemiology

Compared to adults, pericarditis is less frequently encountered in children. Hence, epidemiological data is sparse with reports limited to single center series [15•, 29, 50]. The reported incidence in the general population of acute pericarditis is 30–150/100,000 per year [51, 52] and accounts for < 0.2% to 5% of all emergency department visits for chest pain in children with no prior heart disease [15•, 53, 54]. After the acute episode has subsided, acute pericarditis may recur leading to recurrent pericarditis in 35% of pediatric patients (similar rates in adults) [15•] with rates of recurrence higher if the primary acute episode is not treated with colchicine [1••, 7, 23, 55] or with a rapidly tapered course of corticosteroids [56].

Clinical Manifestations

The presence or absence of symptoms in acute pericarditis is contingent on the specific etiology. In isolated pericarditis, chest pain is typically a central symptom. In the context of a systemic disease, non-cardiac manifestations of the underlying disease process may predominate (e.g., fever, night sweats, arthritis, weight loss, and rash).

In a study of 50 patients with pediatric pericarditis by Perez-Brandao et al. [57•] evaluating admissions to their single center cardiology unit from 2003 to 2015, the most common finding of among their cohort was chest pain (70%), followed by fever (26%), fatigue (18%), and dyspnea (12%). Eight patients (16%) presented with cardiac tamponade, 8% developed pericardial constriction, and 14% of patients

developed recurrence of symptoms. Concomitant myocardial involvement was noted in 17 patients.

Chest pain associated with pericarditis is classically sharp but may also be described as dull, squeezing, or throbbing. It is typically exacerbated while supine and relieved on sitting up and leaning forward. Inspiration and coughing may aggravate the pain, which can also occasionally radiate to the trapezius ridge [11•, 58]. Abdominal pain secondary to hepatic distention can rarely occur, particularly in children, patients with rapidly accumulating effusions [59]. Right-sided and left-sided heart failure symptoms may also result from impaired diastolic filling because of pericardial thickening and scarring in constrictive pericarditis [1••, 60, 61].

A pericardial friction rub can be auscultated on the left lower sternal border and is accentuated with maneuvers approximating the heart to the chest wall, such as having the patient lean forward [62, 63]. Rubs are typically high-frequency, scratching, crunching sounds that can vary in duration from intermittent to throughout the cardiac cycle [11•]. Notably, in patients with large effusions, a rub may be absent [1••, 11•, 64, 65]. In a single center study at a tertiary, pediatric center evaluating clinical presentation of children to the emergency room with pericarditis, the most common symptoms were chest pain (96%), followed by fever (55%) and vomiting (32%). Additional, less frequent symptoms included cough, shortness of breath, and fatigue [15•]. Other etiologies of pediatric chest pain that should be considered include musculoskeletal, psychological, gastrointestinal, and respiratory causes [66].

Constrictive pericarditis manifests with numerous physical examination findings occurring with varying specificities. Jugular venous pressure is elevated and classically increases with inspiration, known as Kussmaul's sign. A pericardial knock, an extra sound occurring in early diastole, is also characteristic, reflecting rapid diastolic filling terminating early. Pulsus paradoxus is frequently present, consistent with ventricular interdependence [67, 68].

Pericardial effusions are generally asymptomatic when small or moderate in size. Clinical examination is often unremarkable in the absence of large pericardial effusion and tamponade. Characteristic features of cardiac tamponade including Beck's triad of muffled heart sounds, jugular venous distension, and hypotension can occur, though a recent study of 153 adults with pericardial effusion or tamponade patients found that only 50% had at least one feature, with none having all three features of the triad [69].

Diagnosis

The diagnosis of acute pericarditis is primarily a clinical diagnosis based on the presence of at least 2 of 4 criteria including chest pain, a pericardial rub, electrocardiographic (ECG) changes, and pericardial effusion [1••, 11•]. The diagnosis of incessant, recurrent, or chronic pericarditis is the same as acute pericarditis but with varying course and duration of symptoms [1••] (Fig. 2). One study showed that recurrent pericarditis can occur in 35% of pediatric patients [15•]. Unlike adults, recurrent pericarditis in children may more commonly present with fevers, elevated inflammatory markers, and pericardial effusion [70].

The evaluation of patients with clinically suspected acute pericarditis should start with electrocardiogram (ECG), chest X-ray, transthoracic echocardiography, and laboratory markers of inflammation and myocardial injury. Clinical presentation and role of additional diagnostic studies may vary based on whether pericarditis is isolated versus part of a systemic disease as well as the duration of symptoms such as acute, subacute, chronic, or recurrent [1••, 64]. Certain clinical indicators on presentation that may be predictive of complication or recurrence include high fever, subacute course, large pericardial effusion, cardiac tamponade, and failure to respond to treatment [71, 72].

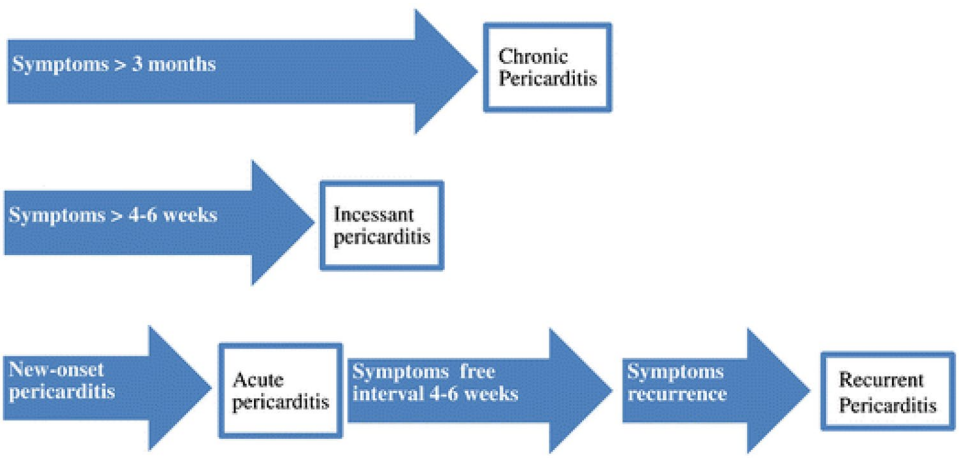

Fig. 2 Classifying pericarditis according to the duration of symptoms (reprinted by permission from Springer Nature: Fardman et al. Curr Cardiol Rep. 2016 May;18(5):46) [98]

ECG changes can occur in pericarditis as a result of inflammation in the epicardium and nearby myocardium, as the parietal pericardium is inert. ECG changes specific for acute pericarditis include widespread ST elevation in most leads and/or PR depression. However, up to 40% of patients may exhibit atypical or non-diagnostic ECG changes. The typical ECG findings, when present, can further evolve throughout the course of illness though these sequential changes are not always seen. In the subacute (second) stage, ST segments may normalize along with T wave flattening. In the third stage, T wave inversion predominates followed by normalization of all changes in stage four [11•, 73]. Differential diagnoses to consider for ST elevation include acute coronary syndromes and early repolarization, with the former less frequently seen in the pediatric population [1••]. A chest radiograph is a useful screening tool to evaluate the cardiac silhouette and cardiothoracic ratio, which can be enlarged in the presence of a significant pericardial effusion. It can also show whether there is pleural or pulmonary involvement [1••, 74, 75].

Trans-thoracic echocardiography (TTE) is the first line imaging test in patients with acute pericarditis and can assist in recognition of patients with higher risk for complications. TTE is ideal as it is easy, quick, and safe to perform as well as widely available [74, 75]. It can accurately identify the presence and size of a pericardial effusion, tamponade physiology, and ventricular dysfunction suggestive of myocardial involvement. Though many patients with acute pericarditis may have normal echocardiography, pericardial brightness or thickening may be visualized. TTE is also valuable in differentiating constrictive pericarditis from restrictive cardiomyopathy. In patients with constrictive pericarditis, TTE can help identify the respirophasic shift of the ventricular septum to the left with inspiration and right with expiration and a "septal bounce" which is secondary to the sudden cessation of ventricular filling from the constrictive pericardium [76]. TTE can also demonstrate tamponade physiology [74]. This complication is less likely to be seen in children with idiopathic or viral pericarditis. In a large multicenter analysis of idiopathic or viral pericarditis in children, tamponade physiology was only seen in 2% of patients [14•]. TTE may be inadequate in detection of loculated effusions or characterization and quantification of the pericardial fluid [1••, 11•].

Computed tomography (CT) and cardiac magnetic resonance imaging (CMR) should be considered in clinical scenarios when echocardiographic findings are inconclusive or complex; atypical clinical features are present. This may include patients who are unresponsive to therapy, with hemodynamic compromise, associated trauma, persistent fevers, or with concern for a secondary cause for pericarditis [74]. CT with contrast is helpful to identify pericardial inflammation, thickening, and calcification, as well as characterization of pericardial fluid (transudative versus exudative). Non-calcified but inflamed pericardium is suggestive of a more acute process, whereas progressive thickening and irregularity may suggest a more chronic process [1••, 11•, 74, 75].

CMR is unique in that it can provide information about morphology and hemodynamics. Specifically, CMR can show tissue characterization of edema and inflammation in both the pericardium and myocardium and cardiac function, as well as cardiac filling and functional consequences of a non-compliant pericardium in those suspected to have constrictive pathophysiology. CMR with late gadolinium enhancement (LGE) has a high sensitivity in detecting inflammation of the pericardium. Moreover, assessment of pericardial inflammation with LGE and pericardial edema in T2-weighted sequences can help determine the stage of inflammation or phase of illness. The presence of LGE and increased T2 signal suggests acute inflammation, while the absence of T2 signal would suggest more chronic inflammation. Notably, CMR is a poor modality for detecting pericardial calcification. The ability to trend the degree and stage of inflammation present can help guide therapy, especially in recurrent pericarditis [1••, 11•, 74, 75]. Ultimately, the clinical context of the patient and safety of the patient to undergo a particular imaging study should guide decision-making on study selection.

As pericarditis and myocarditis may co-exist in 20–30% of patients, cardiac biomarkers including cardiac-specific troponin I, troponin T, or CK-MB elevation can be useful to demonstrate whether there has been concomitant myocardial injury [1••, 64]. Cardiac biomarkers along with assessment of cardiac function by echocardiography or other indicated imaging modality can help establish whether pericarditis or myocarditis predominates. The clinical syndrome of "myopericarditis" generally has a benign course and is characterized by acute pericarditis, elevated markers of myocardial injury, and the absence of focal or diffuse left ventricular dysfunction on echocardiography or cardiac MRI [1••, 11•, 64]. In contrast, "perimyocarditis" is when myocarditis predominates with pericardial involvement; there is new-onset left ventricular dysfunction with elevated myocardial biomarkers along with pericarditis. Accurate characterization of the clinical syndrome can help guide surveillance, treatment, and counseling on return to activity [1••, 11•].

Elevated markers of inflammation including white blood cell count (WBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) can be a supportive finding for acute pericarditis in both adult and pediatric patients. Markedly elevated inflammatory markers can also be predictive of recurrent pericarditis in pediatric patients [27]. The overall trends in inflammatory markers can be helpful in monitoring the activity of the disease and efficacy of treatment [1••, 15•].

Beyond the primary evaluation for pericarditis, additional testing may be warranted if the patient's clinical status suggests a specific cause. If the patient is febrile and there is concern for bacterial infection, blood cultures should be sent. Additional serologic assays should be sent if there is suspicion for an underlying systemic inflammatory condition. If there are hematologic abnormalities and extra-cardiac findings suggestive of cancer, more comprehensive imaging may be warranted [1••, 65]. A large symptomatic pericardial effusion and/or cardiac tamponade may warrant pericardiocentesis with analysis of pericardial fluid, especially when a bacterial or neoplastic process is suspected [64].

Management (Table 2)

NSAIDs

NSAIDs form the cornerstone of management for both acute and recurrent pericarditis in children, with the use of aspirin, indomethacin, ibuprofen, and other agents all previously described in the literature. A recent analysis of the Pediatric Health Information System (PHIS) database of inpatient pediatric hospitalizations across the USA demonstrated that over 70% of initial acute idiopathic pericarditis and pericardial effusion admissions included NSAID therapy, with an additional 7% of patients receiving aspirin as part of their initial management [14•]. A multicenter Italian study of recurrent pericarditis in children and adolescents similarly demonstrated a high proportion of cases receiving treatment with NSAIDs (81%) [26••]. The 2015 European Society of Cardiology Guidelines for the Diagnosis and Management of Pericardial Diseases further stresses the central role of anti-inflammatory therapies in the management of pericarditis: NSAIDs are recommended in the initial management of acute pericarditis (class I recommendation, level of evidence A) as well as in the management of recurrent pericarditis (class I recommendation, level of evidence A) [1••]. As no pediatric-specific guidelines exist, extrapolation of these adult guideline recommendations to the pediatric population is frequently performed.

Steroids

Similar to NSAIDs, corticosteroids are widely used in the management of pericarditis. An analysis of the PHIS database demonstrated that 23% of pediatric patients admitted for pericarditis and pericardial effusions received corticosteroids as part of their index admission [14•]. This percentage was higher in a large Italian multicenter study (65% of cases) [26••]. However, the benefits of using steroids appear mixed. Although rapid clinical improvement in symptomatology and indices of inflammation are often seen, there is concern that use of steroids can contribute to a higher risk of pericarditis recurrence. In fact, in a secondary analysis of the COlchicine for acute PEricarditis (COPE) trial examining the use of colchicine for prevention of pericarditis recurrence in adults, corticosteroid use at index pericarditis episode was found to be an independent risk factor for subsequent pericarditis recurrence [23]. The message from pediatric studies is less clear, as portrayed by one study which demonstrated that while corticosteroid-treated patients experienced double the rate of recurrences compared to those without, these corticosteroid-treated cases were also more likely to be associated with pericardial effusions suggesting they may represent a cohort of patients with more severe disease [26••]. Given the concern that early use of corticosteroids could contribute to a higher rate of later pericarditis recurrence, current adult pericarditis management guidelines recommend avoidance of corticosteroids at initial presentation (class III recommendation, level of evidence C). Corticosteroids do have a part in the management of acute pericarditis as second-line therapy or as initial therapy in patients with contraindications to NSAID and colchicine use, and only after infectious etiologies have been excluded [1••]. An intriguing new application for steroids is in intrapericardial administration: one case report [77] describes the dramatic resolution of incessant pericardial effusion following acute pericarditis once intrapericardial steroids were administered. This patient's disease had previously proved refractory to NSAIDs, anakinra, prior steroid course, aspirin, and anakinra.

Colchicine

Colchicine is an anti-inflammatory agent with a long history of use in conditions such as gout. It concentrates to high levels in leukocytes, and this, coupled with its mechanism of action involving the disruption of microtubules, leads to impaired leukocyte function and decreased inflammatory response [23]. A prospective randomized adult trial (COPE trial) was conducted to explore if colchicine use at first pericarditis occurrence could reduce the rate of recurrences. In 120 adults followed for a mean of 24 months after index pericarditis episode, a three-fold higher recurrence rate was seen in individuals treated with aspirin alone compared to colchicine plus conventional treatment (aspirin or corticosteroids) (33% versus 12%, respectively) [23]. However, concern has been raised in analysis of a large multicenter adult registry that corticosteroid use prior to colchicine may decrease the efficacy of colchicine therapy in preventing future flares of pericarditis [78]. Adult pericarditis guidelines recommend colchicine in the management of acute pericarditis as an adjunct to NSAID therapy (class I recommendation, level of evidence A) as well as in recurrent

Table 2 Management of pediatric pericarditis

Author	Single center/multicenter	Study duration	Main observation	Other important findings
Corticosteroids				
Imazio et al. [26••]	Multicenter cohort study (8 sites, 110 total patients; 65% of patients treated with corticosteroids)	Median follow-up of 60 months	Corticosteroid-treated patients experienced double the rate of recurrences compared to those without (standardized risk of recurrence per 100 patient-years of 93.2 compared with 45.2)	Corticosteroid-treated cases were also more likely to be associated with pericardial effusions, suggesting they may represent a cohort of patients with more severe disease
Othman and Eldadah [77]	Single case report (1 patient)	Follow-up 2 years	Intrapericardial injection of methylprednisolone followed by prolonged oral prednisolone led to resolution of unremitting pericarditis and pericardial effusion	Effusion had been refractory to NSAIDs, anakinra, prior steroid course, aspirin, and anakinra
Colchicine				
Brucato et al. [81]	Single case report (1 patient)	Follow-up 29 months	Colchicine was substituted for steroids in a patient with steroid-dependent recurrent pericarditis with no further relapses	
Imazio et al. [26••]	Multicenter cohort study (8 sites, 110 total patients; 62% of patients treated with colchicine)	Median follow-up of 60 months	Treatment with colchicine associated with significant decrease in the rate of recurrence (3.7 per year to 1.4 per year)	
Raatikka et al. [29]	Multicenter cohort study, 15 patients. 4 patients treated with colchicine	Follow-up time ranged from 4 to 16 years (mean 8 years)	Continued pericarditis recurrences (mean 5.8 in a 13-month period) on colchicine	Nearly half of patients in this cohort (7 of 15) had post-pericardiotomy syndrome
Shin et al. [80]	Single case report (1 patient)	Follow-up 30 months	Colchicine use allowed for freedom from recurrent pericarditis after demonstration of steroid-dependency	
Yazigi et al. [79]	Single center case series, 3 patients with idiopathic recurrent pericarditis	Follow-up of 11, 12, and 18 months	All patients with relief of pericarditis after colchicine initiation and no further recurrences	
IVIG				
del Fresno et al. [97]	Single center case series (2 patients)	Follow-up of 11 and 13 months	IVIG administration allowed for resolution of recurrent pericarditis in children continuing to have recurrences on NSAID, corticosteroid, and colchicine therapies	
Peterlana et al. [89]	Single center case series (1 pediatric patient)	Length of follow-up not specified	IVIG allowed for decrease in total steroid dose required in steroid-dependent recurrent pericarditis	

Table 2 (continued)

Author	Single center/multicenter	Study duration	Main observation	Other important findings
Anti-TNFα				
González et al. [91]	Single center case series (3 patients)	Follow-up of 3, 6, and 8 years	Etanercept use allowed for complete remission of recurrent pericarditis refractory to NSAIDs, steroids, and colchicine in two patients. Third patient had another flare of pericarditis on etanercept, with subsequent remission achieved with adalimumab	All patients diagnosed with idiopathic recurrent pericarditis
Anakinra				
Finetti et al. [88]	Multicenter retrospective cohort (12 children)	Median follow-up 39 months	Use of anakinra was associated with complete remission of disease, persistent control while on therapy, and ability to wean from additional therapies (i.e., steroids and colchicine)	Attempts to wean from anakinra resulted in recurrence of pericarditis in 43% of patients, with all demonstrating resolution of flares with anakinra re-initiation
Imazio et al. [26••]	Multicenter cohort study (8 sites, 12 patients on anakinra)	Median follow-up of 60 months	Use of anakinra associated with a dramatic decrease in the recurrence rate of pericarditis (4.3 recurrences per year to 0.1 per year)	
Picco et al. [85]	Single center case series (3 patients)	2005–2008	Successful treatment of steroid-dependent idiopathic recurrent pericarditis using anakinra in 3 pediatric patients	Ability to wean from steroid therapy with no relapses on anakinra monotherapy in short-term follow-up (3–4 months)
Rodriguez-Gonzalez et al. [86]	Single case report (1 patient)	26-month follow-up	Patient with steroid-dependent recurrent pericarditis able to be weaned from steroid therapy and controlled without recurrence on anakinra monotherapy	
Scardapane et al. [87]	Single case report (1 patient)	12-month follow-up	Patient with steroid-dependent recurrent pericarditis able to be weaned from steroid therapy and controlled without recurrence on anakinra monotherapy	
Canakinumab				
Epçaçan et al. [93]	Single center case report (1 patient)	~4 years of follow-up	Successful remission of recurrent pericarditis with canakinumab after anaphylaxis experienced with anakinra	Patient also maintained on colchicine therapy

Table 2 (continued)

Author	Single center/multicenter	Study duration	Main observation	Other important findings
Signa et al. [94]	Single center case series (2 patients)	2015–2020	Patients with recurrent pericarditis achieving remission with anakinra, with return of pericarditis on canakinumab therapy	Etiologies: 1, idiopathic 1, post-pericardotomy
Pericardiectomy				
Thompson et al. [96]	Single center case series (27 patients)	Median follow-up 1 year	Patients had received an average of 2.2 medications as part of medical pericarditis management prior to surgery. Complete resolution of symptoms achieved in 89% of patients at 1 year	16 patients had inflammatory pericarditis; 11 had constrictive pericarditis. Only one early mortality: acute hepatic failure in a patient with radiation-induced pericardial disease, 155 days after surgery

pericarditis (class I recommendation, level of evidence A) [1••].

Colchicine therapy for treatment of pediatric pericarditis was described initially in case reports, with some descriptions of clinical improvement in pericarditis symptoms and freedom from recurrences [79], with other reports detailing patients continuing to have recurrences of disease even after colchicine addition to corticosteroid therapy [29]. Encouragingly, some reports portrayed colchicine as allowing for the weaning and discontinuation of steroids in individuals with steroid-dependent recurrent pericarditis [80, 81]. The single multicenter description of colchicine use in pediatric pericarditis described it as a frequently used therapy (62% of cases), and that treatment with colchicine was associated with a significant decrease in the rate of recurrence (3.7 per year to 1.4 per year) [26••]. A systematic review on the topic of colchicine for pediatric recurrent pericarditis has been previously published for readers interested in the topic [82].

Anakinra

Anakinra is a non-selective interleukin-1 (IL-1) antagonist that targets both IL-1α as well as IL-1β and is used in the management of a wide range of inflammatory and autoinflammatory conditions. A recent randomized clinical trial (AIRTRIP) explored the effectiveness of anakinra in the management of adult patients with steroid-dependent and colchicine-refractory recurrent pericarditis [83]: patients who achieved remission of recurrent pericarditis while on anakinra were randomized to either continued anakinra treatment or withdrawal with placebo. Continued use of anakinra significantly reduced the recurrence of pericarditis in study patients. While this study focused on an adult population with idiopathic recurrent pericarditis, results are encouraging that a similar effect may be seen in the pediatric population. A larger adult registry of patients with recurrent pericarditis (the majority with idiopathic pericarditis) saw a six-fold reduction in pericarditis recurrence alongside a decreased steroid requirement and a reduction in hospitalizations. Side effects mostly consisted of localized skin reactions [84].

Initial reports of anakinra use for recurrent pericarditis episodes in pediatric patients [85–87] have described dramatic clinical improvement in steroid-dependent and colchicine-refractory cases of recurrent pericarditis, often allowing affected patients to wean from and discontinue steroid therapy. In one multicenter study including 12 children with recurrent pericarditis, use of anakinra was associated with complete remission of pericarditis flares, ability to wean from other therapies such as colchicine and steroids, and prevention of further flares while on anakinra therapy [88]. Another multicenter study of children with recurrent pericarditis described anakinra use in only a small percentage of patients ($n = 12$); however, this treatment modality was

associated with a dramatic decrease in the recurrence rate of pericarditis (4.3 recurrences per year to 0.1 per year) [26••].

Other Agents

Intravenous immunoglobulin (IVIG) use for pediatric pericarditis is limited to case reports, mainly detailing use in conjunction with corticosteroids in the management of flares of recurrent pericarditis [81, 89]. Additional small studies describe IVIG administration allowing for resolution of recurrent pericarditis in children continuing to have recurrences on NSAID, corticosteroid, and colchicine therapies [90].

Tumor necrosis factor-α (TNF-α) blockers represent another intriguing therapeutic target, given their utility in management of a wide range of rheumatologic conditions. Descriptions of TNF-α blocker use in pediatric pericarditis are very limited: one study reported the use of etanercept in two patients allowing for complete remission of recurrent pericarditis refractory to NSAIDs, steroids, and colchicine. A third patient had another flare of pericarditis on etanercept, with subsequent remission achieved with adalimumab [91]. Paradoxically however, there are also reports in the literature of TNF-α blocking agents *causing* acute pericarditis [92], which may limit enthusiasm for more widespread use in the treatment of pediatric pericarditis.

Emerging Therapies: Specific IL-1 Antagonists (Canakinumab and Rilonacept)

Given the effectiveness of anakinra, canakinumab (a selective IL-1β antagonist) has also been utilized in the treatment of refractory pericarditis. This agent may offer some benefit given its longer half-life (21–28 days for canakinumab compared with 4–6 h for anakinra) [93]. Experience with this agent in pediatric pericarditis is limited to two case reports: the first described successful management of recurrent pericarditis with canakinumab in a pediatric patient after anaphylaxis was experienced with anakinra [93]. The second study, however, reported that switching to canakinumab was associated with pericarditis relapse in 2 pediatric patients switched from anakinra [94]. A therapy that is being explored in the adult population is rilonacept, an IL-1α and IL-1β cytokine trap. In a randomized controlled trial of adult recurrent pericarditis, rilonacept was found to quickly resolve recurrent pericarditis and significantly decrease the rate of recurrence compared to placebo; 7 pediatric patients (age < 18 years) were included in the run-in period, and of these, 3 continued to the randomization phase of the trial [95]. Further study of these emerging therapies is needed in the pediatric population.

Interventional Approaches

While drastic, surgical pericardiectomy remains a definitive treatment for pericarditis refractory to medical therapies. An analysis of the PHIS database demonstrated that in the index admission for acute pericarditis and pericardial effusion, 2.0% underwent pericardiectomy [14•]. Reports of pericardiectomy for recurrent and refractory pericarditis are sparse in the pediatric literature and mostly limited to case reports. The largest case series by Thompson et al. [96] details 27 pediatric patients undergoing pericardiectomy at a single center. Patients had received an average of 2.2 medications as part of medical pericarditis management prior to surgery, with steroids, NSAIDs, and colchicine being the most commonly utilized therapies. This series illustrated good short-term success of the surgical intervention, with complete resolution of symptoms achieved in 89% of patients at 1 year.

Conclusion

The etiology for pediatric pericarditis has evolved over the years. With the most recent COVID-19 pandemic, there has been an increasing focus on the effect of the COVID-19 infection as well as mRNA vaccination on pericardial inflammation. Large-scale contemporary epidemiological data regarding incidence and prevalence of both acute and recurrent pericarditis is lacking in pediatrics, and future studies should focus on highlighting this important research gap. Most of the current management strategies for pediatric pericarditis are from experiences gathered from adult data. Pediatric multicenter trials are warranted to understand the best management strategy for those with acute and recurrent pericarditis.

Compliance with Ethical Standards

Conflict of Interest SA is site PI for a multicenter study led by the University of Michigan—reports no salary support. KH reports the following: International Society for Heart and Lung Transplantation (Pediatrics Professional Community Representative to the Early Career and Trainee Committee—2020–present. Unpaid leadership position), International Society for Heart and Lung Transplantation (Co-Chair, Early Career and Trainee Committee—2022–present. Unpaid leadership position), and Advanced Cardiac Therapies Improving Outcomes Network (Co-Chair-VAD Recovery Taskforce, 2022–present. Unpaid leadership position). The other authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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