

# Acute idiopathic pericarditis: current immunological theories

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**Abstract:** Idiopathic recurrent acute pericarditis (IRAP) is a rare disease of suspected immune-mediated pathogenesis. It represents a diagnosis of exclusion. It is necessary to rule out infectious and noninfectious causes of pericardial inflammation, including systemic autoimmune and immune-related disorders, eg, Sjögren's disease, systemic lupus erythematosus. Since pericarditis may precede diagnosis of these disorders, IRAP diagnosis is often made after a long follow-up. According to the two main pathogenetic theories IRAP may represent an organ-specific autoimmune disease or an autoinflammatory disease (AInfD). The main evidence for autoimmunity in IRAP is provided by the detection of serum antiheart and antiintercalated-disk autoantibodies, and the response to anti-inflammatory or immunosuppressive therapy. The findings of familial forms and of proinflammatory cytokines in the pericardial fluid in IRAP would be in keeping with both organ-specific autoimmune disease and AInfD. In fact, AInfD are genetic disorders characterized by primary dysfunction of the innate immune system, due to mutations of genes involved in the regulation of the inflammatory response, in the absence of antigen specific T cells or autoantibodies. In AInfD there are active disease phases with raised non-cardiac specific inflammatory markers, such as C-reactive protein, as well as symptom-free intervals with possible C-reactive protein normalization. A minority of IRAP patients (6%) carry a mutation in the TNFRSF1A gene, encoding the receptor for tumor necrosis factor- $\alpha$ . This suggests that some IRAP patients may have an atypical or subclinical form of AInfD. Thus, IRAP may represent a syndrome with distinct pathogenetic mechanisms in different patients' subsets.

**Keywords:** pericarditis, autoimmunity, autoantibodies, heart disease, immune factors

## Introduction

Pericarditis may account for about 5% of presentations to emergency departments for nonischemic chest pain.<sup>1</sup> Recurrences occur in up to 15%–32% of patients.<sup>2–8</sup> Recurrent acute pericarditis is generally idiopathic or postcardiac injury, and is often a frustrating disease, for both patients and physicians.<sup>2–7</sup> Idiopathic recurrent acute pericarditis (IRAP) is a disease of suspected, yet unproven, immune-mediated pathogenesis. IRAP should not be confused with a pericarditis associated with systemic autoimmune or immune-mediated disorders; all known causes of pericarditis should be excluded.<sup>6</sup> An apparently acute idiopathic pericarditis may precede diagnosis of systemic autoimmune or immune-mediated disorders, thus the diagnosis of IRAP is often made retrospectively after a long follow-up. Here we will review the two main pathogenetic theories, according to which IRAP may represent an organ-specific autoimmune disease (O-s AID) or an autoinflammatory disease (AInfD).

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## IRAP diagnosis

A first attack of acute pericarditis is clinically defined by at least two of the following features: (1) typical chest pain (with or without a pericardial friction rub), (2) suggestive electrocardiogram changes (new diffuse ST-segment elevation or PR-segment depressions), (3) new or worsening pericardial effusion, (4) normal creatine kinase MB (CK-MB) and/or cardiac troponins, with or without increased C-reactive protein (CRP).<sup>9–13</sup> The minimum criteria for diagnosis of recurrences include typical pericardial chest pain and one or more of the following features: (1) pericardial friction rub, (2) suggestive electrocardiogram abnormalities, (3) pericardial effusion on echocardiography or cardiovascular magnetic resonance, (4) high white blood cell count, CRP, or erythrocyte sedimentation rate.<sup>9–13</sup> After a first relapse, there is an increased recurrence rate, particularly if the patients were treated with steroids.<sup>2,8</sup>

According to current guidelines, etiopathogenetic diagnosis in acute pericarditis should be based upon pericardial/epicardial biopsy findings.<sup>6</sup> Idiopathic, eg, immune-mediated, pericarditis is defined by: (1) failure to identify genomes from cardiotropic viruses and other infectious agents by molecular techniques, mainly polymerase chain reaction (PCR) in the pericardial fluid and/or on pericardial/epicardial biopsy, (2) presence of bound immunoglobulin on pericardial/epicardial biopsy, (3) detection of antiheart muscle antibodies in the pericardial fluid, (4) exclusion of other known causes of pericardial inflammation.<sup>6</sup> Some experts advocate that, once collagen vascular disease, previous cardiac surgery, or myocardial infarction are ruled out, relapsing pericarditis is probably immune-mediated with or without a viral trigger.<sup>4,5,7,11–14</sup> Pericardial biopsy is not widely used.<sup>4,5,7</sup> IRAP has a benign prognosis,<sup>1,10–13</sup> thus an invasive approach is often not undertaken, at least in the majority of patients.<sup>4,5,7</sup>

However, the main drawbacks of such a conservative approach are that: (1) etiology and pathogenesis of IRAP remain controversial, (2) viral etiology is often suspected, but not proven, and its role as a trigger or precipitating factor in IRAP remains undefined. The most frequently involved as well as rare infectious and noninfectious agents are summarized in Table 1. Studies using pericardioscopy, epicardial biopsies, and PCR identified the following infectious agents: mainly viruses (coxsackievirus A and B1–4, Echovirus 8, mumps, Epstein–Barr virus, cytomegalovirus, varicella, rubella, human immunodeficiency virus-1, parvovirus B19); bacteria (most commonly tuberculosis, then rarely pneumococcus, meningococcus, hemophilus,

*Treponema pallidum*, borreliosis, chlamydia, *Providencia stuartii*); fungi (*Candida*, *Histoplasma*) and parasites (*Entamoeba histolitica*, *Echinococcus*, *Toxoplasma*).<sup>6,14</sup>

The most commonly reported specific etiologies include tuberculosis (3.9%–4.7%), neoplastic pericarditis (4.7%–7%), and autoimmune disease (1.7%–10.2%).<sup>1–14</sup> Acute pericarditis is presumed to be idiopathic and/or viral in 80%–90% of the cases in immunocompetent patients from developed countries.<sup>1–15</sup> Immune-mediated pericarditis may include: allergic (eg, drug-related), autoimmune (IRAP, postmyocardial injury syndromes, and pericarditis associated with systemic autoimmune disease), and autoinflammatory forms (eg, pericarditis in association with familial Mediterranean fever) (Table 1).

## Is IRAP as an O-s AID?

Autoimmune diseases in humans fulfill at least two of the major criteria proposed by Rose and Bona.<sup>16</sup> The involvement of organ-specific autoimmunity in IRAP is suspected, but not yet fully proven. Some indirect evidence is the presence of pro-inflammatory cytokines such as interleukin-6 (IL-6), IL-8, and interferon-gamma in the pericardial fluid, but not in plasma, which suggests a local inflammatory reaction.<sup>17</sup> However, the findings of familial forms and of proinflammatory cytokines in the pericardial fluid in IRAP would be in keeping with both O-s AID and AInfD (Table 2). Anti-nuclear antibodies have been detected in 43.3% of IRAP patients, in comparison to 9.8% of healthy controls, and anti-nuclear antibodies might be markers of nonorgan-specific autoimmune disease.<sup>18</sup> Importantly, IRAP typically shows a good response to anti-inflammatory or immunosuppressive therapies.

The recent detection of serum antiheart (AHA) and anti-intercalated-disk antibodies (AIDA) is the strongest evidence in support of the autoimmune hypothesis in IRAP.<sup>19</sup> In particular Caforio et al<sup>19</sup> reported a high frequency of AHA of the cross-reactive 1 type and of AIDA by indirect immunofluorescence (IF) in patients with IRAP compared to non-inflammatory heart disease, ischemic heart failure, and normal control subjects. This finding is in keeping with an autoimmune component of the disease in at least 55% of patients. Conversely, frequencies of the organ specific and cross-reactive 2 types were similar in IRAP and controls. In biopsy-proven myocarditis and in dilated cardiomyopathy, organ specific and cross-reactive 1 types, as well as AIDA are increased compared to disease and normal control groups.<sup>20–23</sup> The authors provided possible explanations for the discrepancy.

**Table 1** Etiopathogenetic agents associated with pericarditis

<b>1. Infectious pericarditis</b>	
Bacterial	Most common: <i>Mycobacterium</i> (tuberculosis) (4%–5%); other rare agents: <i>Pneumococcus</i> , <i>Meningococcus</i> , <i>Gonococcus</i> , <i>Hemophilus influenzae</i> , <i>Staphylococcus</i> , <i>Streptococcus</i> , <i>Mycoplasma pneumoniae</i> , <i>Neisseria meningitidis</i> , <i>Neisseria gonorrhoeae</i> , <i>Legionella</i> , <i>Listeria</i> , <i>Providencia stuartii</i> , <i>Chlamydia</i>
Spirochetal	<i>Borrelia</i> (Lyme disease), <i>Leptospira</i> (Weil disease)
Fungal	rare: <i>Histoplasma</i> (immunocompetent patients), <i>Blastomyces</i> , <i>Candida</i> , <i>Aspergillus</i> (mainly immunosuppressed patients)
Protozoal	Rare: <i>Toxoplasma gondii</i>
Parasitic	Rare: <i>Echinococcus granulosus</i> , <i>Entamoeba histolitica</i>
Rickettsial	Rare: <i>Coxiella burnetii</i> (Q fever)
Viral	Presumed most common: coxsackievirus A and B1–B4, echovirus, human herpes virus-6; rare: hepatitis viruses, influenza A and B viruses, cytomegalovirus, Epstein–Barr virus, adenovirus, varicella-zoster, rubella virus, mumps virus, parvovirus B19, human immunodeficiency virus-1
<b>2. Immune-mediated (noninfectious) pericarditis</b>	
Allergic	Tetanus toxoid, vaccines, serum sickness, drugs (rare): procainamide, hydralazine, isoniazid, and phenytoin (lupus-like syndrome), penicillin (hypersensitivity pericarditis with eosinophilia), doxorubicin, and daunorubicin (more often associated with a cardiomyopathy)
Autoimmune	IRAP Pericardial injury syndromes (post-myocardial infarction, postpericardiectomy, posttraumatic and iatrogenic, eg, post-percutaneous coronary intervention, post-pacemaker insertion, postablation) Associated with autoimmune disorders: (most common) systemic lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis, systemic sclerosis, systemic vasculitis, Behçet's syndrome, sarcoidosis (Rare) familial Mediterranean fever, TRAPS
<b>3. Noninfectious, nonimmune pericarditis</b>	
Primary neoplastic	(Rare; most frequent pericardial mesothelioma)
Secondary neoplastic	(Common; most frequent lung and breast cancer, lymphoma)
Metabolic	(Common: uremia, myxedema; others rare)
Traumatic	Direct injury (penetrating thoracic injury, esophageal perforation, iatrogenic) Indirect injury (no penetrating thoracic injury, radiation injury)

**Abbreviations:** IRAP, Idiopathic recurrent acute pericarditis; TRAPS, Tumor necrosis factor receptor-associated periodic syndrome.

Firstly, IRAP sera were tested at last follow-up, after a long history of symptoms and following several immunosuppressive therapies, which may have lead to epitope spreading and change in cardiac antigen specificities. Anyhow, the cross-reactive 1 type has partial cardiac specificity and is also more frequently found in immune-mediated myocarditis or dilated cardiomyopathy than in controls.<sup>20–23</sup> Secondly, it is not known if myocarditis was associated with IRAP. The inflammatory process of acute pericarditis may involve the

epicardium and cause myocardial damage, as reflected by CK-MB and troponin release.<sup>24</sup> None of the study patients had echocardiographic findings suggestive of myocardial involvement (regional or global wall motion abnormalities, increased wall thickness) or increased CK-MB, at diagnosis or during follow-up, but endomyocardial biopsy was not performed. Since the diagnosis of myocarditis is based upon established histological, immunological, and immunohistochemical criteria on endomyocardial biopsy, myocarditis cannot be

**Table 2** Clues to autoimmune or autoinflammatory pathogenesis in IRAP

	Autoimmune IRAP	Autoinflammatory IRAP
Presence of autoantibodies (ANA, AHA, AIDA)	+	–
Proinflammatory cytokines in the pericardial fluid	+	+
Autoinflammatory gene mutations	–	+
Familial clustering	+	+
Spontaneous periodic clinical course not related to therapy	–	+
Good response to anti-inflammatory or immunosuppressive therapies	+	+

**Abbreviations:** IRAP, idiopathic recurrent acute pericarditis; ANA, antinuclear antibodies; AHA, antiheart antibodies; AIDA, anti-intercalated-disk antibodies.

theoretically excluded.<sup>25</sup> However, typical acute pericarditis findings such as those described in the study for the first episode were uncommon in a recent large prospective series of biopsy-proven myocarditis.<sup>23</sup> In addition, biopsy-proven myocarditis leads to death or heart transplantation in 27% of patients at 6 years;<sup>23</sup> conversely, IRAP has a documented benign prognosis.<sup>1,10–13</sup> Thus, the authors suggested that myocarditis was unlikely to be present in IRAP patients. Since in autoimmune disease different antibody specificities are associated with distinct clinical phenotypes,<sup>16</sup> the cross-reactive 1 antibody may be more prevalent as a marker of pericardial involvement, the organ-specific type of myocardial autoimmune disease. This view is supported by earlier reports of serum cross-reactive AHA in other forms of suspected immune-mediated pericarditis, eg, the post-pericardiectomy syndrome or the Dressler's syndrome.<sup>26,27</sup>

Autoantigens recognized by the AHA detected by IF in DCM/myocarditis include  $\alpha$  and  $\beta$  myosin heavy chain and myosin light chain-1v isoforms.<sup>28–30</sup> So far the antimyosin antibodies in myocarditis/DCM have been shown to be disease-specific.<sup>28–30</sup> It is presently unknown whether these autoantigens are also responsible for the AHA found in IRAP. The autoantigen(s) responsible for the AHA have not yet been identified, but several monoclonal antibodies to distinct components of the intercalated disk give the same IF pattern, thus there are many candidate autoantigens.<sup>31</sup> The search for additional antibodies in IRAP should be extended using pericardial substrate, though it is very cumbersome to obtain normal pericardial tissue for analysis.

AHA and/or AIDA frequency was high in spite of a long duration of symptoms and of previous anti-inflammatory and/or immunosuppressive therapies.<sup>19</sup> It is likely that the antibody markers are more prevalent in the index episode. Another finding of this retrospective study was the association of positive AIDA status with a high number of relapses, hospitalizations, and more refractory symptoms, in keeping with high immune activation during the “hot” phases of pericardial inflammation.<sup>19</sup> This further reinforces the autoimmune hypothesis in IRAP. Whether or not AIDA may provide useful serum predictors of IRAP relapses and/or guide immunosuppressive therapy warrants future assessment by prospective studies.

## Is IRAP an AInfD?

According to a more recent pathogenetic hypothesis, IRAP may represent an AInfD. These conditions constitute a group of genetic disorders characterized by primary dysfunction of the innate immune system. AInfD is caused by

pathogenic mutations of genes involved in the regulation or activation of the inflammatory response, in the absence of detectable antigen specific T cells or autoantibodies.<sup>32</sup> The most common autoinflammatory syndromes include familial Mediterranean fever (FMF) and tumor necrosis factor receptor-associated periodic syndrome (TRAPS). Recurrent pericarditis is common in FMF or in TRAPS, but an isolated pericardial involvement, typical of IRAP, is rare. Familial clustering is a common feature of both O-s AID and AInfD (Table 2).<sup>33–35</sup>

FMF is an autosomal recessive disease largely confined to distinct ethnic groups from the Mediterranean basin or the Southern Caucasian areas, in particular Sephardic Jewish, Armenian, Arab, Turkish, and Italian populations.<sup>36</sup> It presents at all pediatric ages with recurrent and self-limited (1 to 3 days) attacks of fever in association with mostly sterile peritonitis, synovitis, and pleuritis.<sup>36</sup> Erysipeloid erythema of lower extremities is a distinctive feature.<sup>36</sup> Although pericardial inflammation has generally been considered rare in FMF, some IRAP patients might have in fact FMF, particularly in populations where FMF is more prevalent. The diagnosis of FMF is difficult and based on clinical findings, ethnicity, and good response to colchicine. Cloning of the identified FMF gene (MEFV) provides a new genetic diagnostic tool in FMF.<sup>37</sup> Four missense mutations were reported in 85% of FMF carrier chromosomes.<sup>38</sup> Brucato et al tested 23 Italian IRAP patients and found no common FMF mutations.<sup>39</sup>

TRAPS, the most common autosomal dominant disorder among AInfD, is caused by mutations in the TNFRSF1A gene, encoding the receptor for tumor necrosis factor (TNF)- $\alpha$ .<sup>40</sup> Systemic inflammation in TRAPS may relate to various mechanisms. These include abnormal receptor expression, trafficking, or misfolding and retention in the endoplasmic reticulum, defective cleavage of the TNFRSF1A ectodomain with abnormal signal transduction. All these pathways lead to persistent cellular stimulation induced by TNF- $\alpha$ .<sup>36</sup> Clinical presentation in patients with TRAPS, with onset from late infancy to adulthood, include long-lasting (1–3 weeks) recurrent fever episodes associated with skin rash, arthralgia, migrating myalgia, abdominal pain, and polyserositis, including pericarditis.<sup>41</sup> Patients with TRAPS more often respond poorly to colchicine, but the single attack is responsive to corticosteroids.<sup>42</sup> Of interest, subjects carrying low-penetrance TNFRSF1A mutations may have a late disease onset, shorter febrile episodes, less intense disease-associated systemic signs and symptoms and an isolated recurrent pericarditis, with a periodic course in which the single recurrences are not

strictly related to previous discontinuation of therapy.<sup>41</sup> Thus it seems possible that some IRAP patients may have TRAPS.<sup>33</sup> In keeping with this observation, in a recent study by Cantarini et al TRAPS mutations were detected in about 6% of IRAP patients (8/131 patients).<sup>33</sup> In a multicenter study features associated with detection of TRAPS mutations in IRAP included: positive family history for pericarditis and/or recurrent fever syndrome, relapses occurring years after the first year from disease onset, colchicine failure, and need of immunosuppressive agents.<sup>43</sup>

## IRAP therapy

A complete etiological search in acute pericarditis is rarely undertaken. Thus, the mainstay of therapy in presumed IRAP is empiric control of symptoms by high dosage nonsteroidal anti-inflammatory drugs (NSAIDs) (aspirin at a dosage of 2–4 g daily, indomethacin at 75–150 mg daily, ibuprofen from 1600–2400 mg daily, or diclofenac at 150–200 mg daily probably until CRP normalization).<sup>44–46</sup> Prevention of relapses is accomplished by colchicine (1.0 to 2.0 mg for the first day followed by a maintenance dose of 0.5 to 1.0 mg daily for 6 months) in association with NSAIDs.<sup>44–46</sup> Corticosteroids and immunosuppressive agents may be used in refractory cases.<sup>47–49</sup> Relapses may occur during reduction of drug doses or after discontinuation of treatment. These may arise due to insufficient dose or/and duration of NSAIDs, too rapid tapering of corticosteroids, real reactivation in autoimmune forms, or true reinfection.<sup>44</sup> It seems possible, though unproven, that in viral forms inappropriate early corticosteroid treatment may be a risk factor for relapse or disease prolongation.<sup>44</sup>

Pericarditis is generally an intense inflammatory disease leading to elevation of circulatory inflammatory markers.<sup>12</sup> CRP is one of these markers. CRP serum or plasma levels rise as an unspecific response to inflammatory noxae. CRP is under transcriptional control by cytokines, in particular IL-6.<sup>50</sup> When the stimulus for increased production ceases, CRP concentration falls rapidly.<sup>50</sup> In a prospective study, Imazio et al demonstrated high CRP in the majority of acute pericarditis cases at presentation; in some patients, CRP was initially normal but increased later.<sup>13</sup> This study showed that normal CRP at presentation may be associated with previous empirical anti-inflammatory therapy. In addition it was suggested that high CRP at presentation, if available, is valuable to guide the length of therapy. Thus, dosing and serial weekly monitoring of CRP seem warranted to prevent an early withdrawal of the attack dose.<sup>13</sup> After CRP normalization, tapering may be considered. Persistent CRP elevation,

use of corticosteroids and incomplete response to medical therapy are considered risk factors for recurrence.<sup>13</sup>

Colchicine was introduced in idiopathic pericarditis because of its efficacy in FMF. This drug was shown to reduce relapses in patients with a first episode of acute pericarditis of nonspecific etiology, recruited in the randomized COLchicine for acute PERicarditis (COPE) trial.<sup>8</sup> Colchicine was also efficacious in IRAP patients, included in the COLchicine as first choice therapy for REcurrent pericarditis (CORE)<sup>2</sup> and in the Colchicine for Recurrent Pericarditis (CORP) trials.<sup>46</sup> Similarly it was beneficial in patients at risk of postpericardiotomy syndrome, recruited in the Colchicine for the Prevention of the Post-pericardiotomy Syndrome (CORPS) study.<sup>51</sup> Colchicine binds to  $\beta$ -tubulin, forming tubulin-colchicine complexes. Such complexes seem to inhibit microtubule self-assembly in inflammatory cells, thus potentially affecting several cellular functions, such as chemotaxis, degranulation, and phagocytosis. The anti-inflammatory effect mediated by colchicine may be beneficial both in autoimmune and autoinflammatory IRAP subsets, but the drug is not effective in TRAPS.<sup>43</sup>

High corticosteroid doses (prednisone 1–1.5 mg/kg/daily) were successfully used in selected refractory cases in a small observational trial.<sup>47</sup> Corticosteroids could delay viral clearance and promote recurrences in viral forms. Indeed recent studies<sup>2,8</sup> suggested that the use of corticosteroids is an independent risk factor for relapse. This finding may reflect the empirical use of steroids without ruling out active viral pericarditis according to guidelines (eg, by PCR on pericardial fluid and/or on pericardial biopsy).<sup>6</sup> However, lower doses of steroids, eg, prednisone 0.2–0.5 mg/kg/daily, are employed to treat serositis in various rheumatologic conditions. Similarly, they may be necessary in selected IRAP cases, refractory to NSAIDs, to control symptoms and reduce recurrences and hospitalizations. Tapering should be done slowly over several months, after symptoms resolution and CRP normalization. If symptoms recur, every effort should be done not to increase again corticosteroids, but to control symptoms with NSAIDs plus analgesics.<sup>48</sup>

In refractory cases, eg, those requiring unacceptably high chronic dosages of corticosteroids (higher than 15–20 mg/day) for symptom control, several immunosuppressive or immunomodulatory drugs have been employed, in particular azathioprine, cyclosporine, methotrexate, hydroxychloroquine, high dose intravenous immunoglobulins, and cyclophosphamide.<sup>47,49</sup> Azathioprine (at a dosage of 2–3 mg/kg/day) has been most often used. In general, less toxic and less expensive drugs are preferred, tailoring therapy to the individual patient as well as to the physician's preference.<sup>45</sup>



Three pediatric IRAP cases were treated, during hot phases, defined as acute attacks requiring high dosage of corticosteroids, with the interleukin-1 $\beta$  receptor antagonist anakinra, with immediate response.<sup>52</sup> Anakinra and anti-TNF agents may be an option in patients who do not tolerate or are refractory to other therapies, as well as in the rare patients with TRAPS mutations, but prospective studies are needed.<sup>36</sup>

## Conclusion

The two major immunological theories to explain IRAP suggest that it may be an autoimmune or an autoinflammatory disease. For both theories some evidence has been found and both would be in keeping with the main features of IRAP, in particular the hot phases of pericarditis, the tendency to relapse and the clinical response to anti-inflammatory and/or immunosuppressive drugs (Table 2). More research is needed on this rare and elusive condition. IRAP may represent a syndrome with different pathogenetic mechanisms in distinct subsets of patients, and a distinct response to therapy in relation to the pathogenetic mechanisms involved. The present data seem to indicate that only a minority of IRAP patients may have an AInFD, but more correlative studies in patients with genetic and autoimmune serology characterization would be of great interest.

## Disclosure

The authors report no conflicts of interest in this work.

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