Noninfectious pericarditis: management challenges for cardiologists

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Noninfectious pericarditis: management challenges for cardiologists

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Abstract

The aim of review is to deal with management challenges related either to diagnosis or therapy of non-infectious pericarditis. In European countries with a low prevalence of tuberculosis, the aetiology search is essentially aimed at the exclusion of most common causes, that may require a specific therapy and are at increased risk of complications: systemic autoimmune or autoinflammatory conditions, post-cardiac injury syndrome (5-20%), neoplastic pericardial involvement (5-10%), tuberculosis (about 5% of cases), and rarely purulent in <5%. In developing countries with a high prevalence of tuberculosis, this is the most common cause of pericardial diseases. The diagnosis is based on clinical criteria (pericarditis chest pain, pericardial rubs) integrated with laboratory (elevation of C-reactive protein), and instrumental findings (ECG, echocardiography and imaging evidence of pericardial inflammation in doubtful cases). Poor prognostic predictors (high fever>38°C, subacute course, large pericardial effusion, cardiac tamponade, and lack of response to empiric anti-inflammatory therapies) identify high-risk patients to be admitted for aetiology search and therapy. The mainstay of medical therapy of non-infectious pericarditis is based on NSAID and colchicine, with the possible adjunct of corticosteroids at low-moderate doses for unresponsive patients. Additional therapies, especially anakinra, have been implemented for those who develop corticosteroid dependence and are colchicine-resistant. The most common and troublesome complication of pericarditis is represented by recurrences, while the risk of developing constriction is related to the aetiology and not to the number of recurrences.

**Key words:** pericarditis; recurrence; diagnosis; therapy; colchicine, corticosteroids, anakinra.
**Introduction**

Acute and recurrent pericarditis are relatively common inflammatory diseases of the pericardium, that can occur either as isolated condition or associated with a systemic disease (e.g. inflammatory systemic diseases, renal failure).[1-4] The aetiology of pericarditis may be either infectious or non infectious (Table 1).[3,5] In countries with a low prevalence of tuberculosis, the main causes of infectious pericarditis are represented by cardiotropic viruses (e.g. Enteroviruses, Herpes Virus, mainly EBV and CMV, Parvovirus B 19).[3,6] Often the infectious aetiology is only presumed by exclusion of other more common causes, since the definitive diagnosis would require a pericardial biopsy, that is not warranted in most cases with a self-limiting and benign course. Serology is often used in clinical practice for a presumptive aetiological diagnosis, but simply confirms the presence of a recent viral infection (e.g. by titres of IgM antibodies) or previous viral infection (e.g. by titres of IgG antibodies) without providing a definitive diagnosis of pericardial infection.[3] In countries with a high prevalence of tuberculosis, this disease is the main cause of pericarditis, often exudative with a high risk of evolution into constrictive pericarditis. On this basis, all over the world, tuberculosis is the main cause of pericardial diseases, always to be considered and ruled out especially in immigrants or immunodepressed patients.[3,6]

This review will focus on non-infectious pericarditis and will also include the management of “idiopathic pericarditis”, that is pericarditis without a known aetiology after a proper diagnostic work-up according to 2015 ESC guidelines.[3] The aim of review is to deal with management challenges for cardiologists related to diagnosis and therapy. In order to provide a comprehensive and updated paper, several electronic databases (Pubmed, Cochrane Library, MEDLINE, EMBASE, Scopus, Google Scholar) have been reviewed using the terms “pericarditis” and “diagnosis” or “therapy” from inception through April 2020.

**Aetiology search challenges**

In European countries with a low prevalence of tuberculosis, the aetiology search is essentially aimed at the exclusion of most common causes (Table 2).[7-11] that may require a specific therapy
and are at increased risk of complications: systemic autoimmune or autoinflammatory conditions,[12] post-cardiac injury syndrome (5-20%),[13] neoplastic pericardial involvement (5-10%),[7-11, 14] tuberculosis (about 5% of cases),[6,11] and rarely purulent in <5%. Even when a systematic aetiological search is conducted, most cases remain uncomplicated and “idiopathic” or presumed viral/post-viral.[5] In these settings, if pericarditis is self-limiting and responsive to empiric anti-inflammatory therapies, it is not recommended to perform additional diagnostic testing since management is unchanged.[3] The diagnosis of the specific viral agent would require the demonstration of the infectious agent directly in the pericardium (pericardial biopsy) or pericardial fluid (pericardiocentesis), since viral serology can be useful only to diagnose a recent viral infection without a clear evidence of pericardial infection. Invasive testing with pericardiocentesis has generally a low diagnostic yield in the absence of cardiac tamponade or with moderate to large pericardial effusions with suspicion of a bacterial or neoplastic aetiology.[3,5,15]

**Diagnostic issues**

In clinical practice the diagnosis of pericarditis is based on clinical criteria that have been formulated in early prospective studies.[7,8,10,16] These clinical criteria have been endorsed by 2015 ESC guidelines and include: (1) pericarditis chest pain, (2) pericardial rubs, (3) suggestive ECG changes (widespread PR depression and ST elevation as early signs), and (4) new or worsening pericardial effusion.[3] At least 2 of these 4 criteria should be present in order to reach a definitive clinical diagnosis of pericarditis (Table 3). However, in clinical practice, the relative frequency of these clinical criteria varies according to presentation times and setting (acute vs. recurrent pericarditis). In acute or recurrent pericarditis, pericarditic chest pain is reported in the majority of patients, and it is the usual reason for presentation, while other findings are more common in acute forms, and not during recurrences. For instance, pericardial rubs have been reported in 1/3 of cases in acute pericarditis,[7,8,10,16] but are uncommon for recurrences. The same is also true for ECG changes: widespread ST elevation is usually associated with some degree
of myocardial involvement (>60% of cases with concomitant myocarditis) but less common in simple pericarditis, since the pericardium is electrically silent, and ECG changes reflect myocardial involvement.[17,18] The typical ECG evolution in four stages (Figure 2) is also rare in recurrences and depends on presentation times: ST-elevation can be seen in early stages, especially with concomitant myocarditis but it is less common in late presentations, where only atypical ST-T changes can be documented and even a normal ECG does not exclude pericarditis by itself.[3] Pericardial effusion is reported in 50-60% of cases of acute pericarditis but it is less common in recurrences. Moreover pericardial effusion can be reported even in the absence of pericarditis (e.g. uraemia, hypothyroidism, systemic inflammatory diseases, heart failure, pulmonary hypertension, cancer), and thus it is not essential for the diagnosis of pericarditis, that is “dry pericarditis” in at least 50% of cases.[19,20] On this basis, 2015 ESC guidelines include additional supporting criteria for the clinical diagnosis, that can be used when traditional ones are not sufficient to reach the diagnosis: (1) biomarkers (especially elevation of C-reactive protein).[3,21] and (2) evidence of pericardial inflammation by imaging (CT and cardiac magnetic resonance, since basically the inflamed pericardium is neovascularized and can be contrast-enhanced)[3,22] (Figure 1).

**Triage and admission criteria**

Patients with a specific aetiology (non viral or idiopathic) are at greater risk of complications (recurrences, cardiac tamponade, and constriction). Some clinical features at presentation can be used to predict the increased risk of non-idiopathic and complications. These features are poor prognostic predictors and include: high fever (> 38°C, HR 3.6), unusual for uncomplicated viral or idiopathic pericarditis, subacute course (without an acute onset or without pericarditis chest pain, HR 4.0), large pericardial effusion (> 20mm as largest telediastolic echo free space) or cardiac tamponade at presentation (HR 2.1-2.5), and failure to respond to empiric anti-inflammatory therapy with aspirin or a NSAIDs (HR 2.5-5.5). Female gender has an increased risk of developing complications or having a non-idiopathic aetiology of pericarditis (HR 1.6-1.7).[10,16] According
to experts opinion, additional features to be considered as potential risk factors include: concomitant myocarditis (these patients are admitted for differential diagnoses evaluation, and monitoring of the response to medical therapies), recent chest trauma, use of oral anticoagulants, and immunosuppression conditions. [3,23,24]

Since patients without any of these features have usually a benign, often self-limiting course responding to empiric anti-inflammatory therapies, there is no reason to admit all patients with pericarditis. According to available evidence and guidelines,[3] patients with pericarditis can be submitted to a simple triage at presentation, based on the presence or absence of poor prognostic predictors (Figure 2).[3,23,24] On this basis, patients are divided into: high risk cases (if at least one poor prognostic predictor is present), and non-high risk cases (without any poor prognostic predictor). Patients at high risk are admitted for aetiology search and monitoring of the response to therapy.[3,5] Patients without poor prognostic predictors are treated as outpatient with empiric anti-inflammatory therapy and a planned follow up after 1-2 weeks in order to assess the response to therapy, results of essential blood tests (e.g. blood cell count, C-reactive protein, transaminases, creatinine, CK), and perform an echocardiogram to evaluate the presence of pericardial effusion and additional possible echo signs of constriction. Patients responding to medical therapy are considered at low risk and, if asymptomatic without relapses, may not require additional testing. Patients without full response to medical therapy at 1-2 weeks should be reassessed for admission or additional testing for aetiology search and alternative therapies.[3,10,16]

**Treatment issues**

Although the treatment is also for pericarditis aimed at the cause (e.g. a systemic inflammatory disease, cancer), in clinical practice, the majority of cases of non-infectious pericarditis remains “idiopathic” after aetiology search.[25,26] For this patients the cornerstone of medical therapy is non-steroidal anti-inflammatory drugs (NSAIDs) plus colchicine on top, in order to control symptoms and prevent recurrences.[3,25-28] Colchicine added on top of NSAIDs can halve the
recurrence rate in either acute or recurrent pericarditis (Figure 3)[29-35] and in now registered in several European countries for this indications (e.g. Italy, Austria). The use of colchicine is a class I, LOE A indication for acute and recurrent pericarditis in 2015 ESC guidelines.[3] In clinical practice, it is important to avoid loading doses, considering weight adjusted doses to reduce possible gastrointestinal side effects, that are the main side effects to limit its tolerability (Table 4).

Corticosteroid therapy has been associated with an increased risk of recurrences,[36] if used early and with high doses, however at low to moderate doses (e.g. prednisone 0.2-0.5 mg/kg/day)[37] has specific indications: (1) contraindications and failure of NSAID, specific diseases already on maintenance therapy or with indication to corticosteroids (e.g. vasculitis or systemic inflammatory diseases)[12], concomitant physiological conditions (e.g. pregnancy)[39] or diseases (e.g. renal failure), or therapies (e.g. oral anticoagulants) (Figure 4).

In case of failure of NSAID, colchicine and corticosteroids, a third level of treatment (Figure 5) is represented by triple therapy with a combination of the 3 drugs (a NSAID plus colchicine and low-moderate dose of a corticosteroid).[3,40]

For patients with corticosteroid dependent (unable to taper or withdraw corticosteroids without a new recurrence) and colchicine resistant pericarditis, there are 3 published alternatives (Table 4): azathioprine[41] and human intravenous immunoglobulins (hIVig)[42] for those without evidence of systemic inflammation (no fever and/or C-reactive elevation) or anakinra,[43] a non selective anti IL 1 agent (Figure 6), especially indicated for those with evidence of systemic inflammation by means of fever at each recurrence and/or elevation of C-reactive protein. The evidence to support azathioprine, an old and cheap immunosuppressive drug, and hIVIg is limited by cases report or limited case series.[41,42] On the contrary, there is more evidence to support the use of anakinra by case series,[43,44] a single RCT[45] and more recently an International registry of treated cases.[46]

The last option for the treatment of refractory recurrent pericarditis, when all medical therapies have failed, is represented by pericardiectomy.[47]
Risk of complications

The most common and troublesome complication of pericarditis is represented by recurrences, that have been reported in 20-30% of patients after a first episode of pericarditis, if not treated by colchicine.[29,33] The recurrence rate is higher in patients with recurrent idiopathic pericarditis (30-50%), but can be halved by the regular use of colchicine.[30-32] Other possible complications include cardiac tamponade, that is uncommon (< 2%) in the absence of a specific cause when can raise especially in cases secondary to cancer.[48] Constrictive pericarditis is the most feared complications for clinicians and patients.[49] The common belief is that the risk is correlated with the number of recurrences: the higher the number of relapses, the higher the risk of constriction. However, no cases of constrictive pericarditis have been reported after idiopathic recurrent pericarditis,[50] that is pericarditis without an identified cause. The risk of developing constrictive pericarditis is related to the cause of pericarditis: low risk (< 1%) in patients with idiopathic or viral pericarditis, intermediate risk (3-4%) for those with autoimmune diseases, post-cardiac injury syndromes, and related to cancer, and high risk (20-35%) for bacterial aetiologies (especially tuberculous and purulent pericarditis).[48]

Conclusions

Pericarditis remains challenging especially when complicated and recurrent. Diagnostic and triage criteria have been implemented in clinical practice allowing to reduce hospitalization and management costs. Recently, current available therapies have been improved by the adjunct of colchicine, and anti IL1 agents, such as anakinra for corticosteroid dependent and colchicine resistant cases. However, additional research is needed to better clarify the pathophysiology of recurrences in order to develop more targeted and individualized treatments.
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Figure 1. Main manifestations, and diagnostic criteria for pericarditis.
Figure 2. Triage of pericarditis (see text for comments).
Figure 3. Main clinical trials[29-33] of colchicine in acute and recurrent pericarditis show that recurrence rates have been halved by colchicine in colchicine-treated patients (red bars) on top of other anti-inflammatory drugs (NSAIDs or corticosteroids) compared with those not treated with colchicine or treated with placebo (blue bars) during long term follow-up up to 18 months.
Corticosteroids: 2° Level (LOE B)
Low to moderate doses
(e.g. prednisone 0.2-0.5 mg/kg/day) with slow tapering

The 5 indications to corticosteroids in pericarditis

- Specific diseases (e.g. rheumatological conditions on steroids)
- As combined therapy (with NSAID/colchicine) for recurrences
- Contraindications or failure of ASA/NSAID
- Specific physiological conditions or concomitant diseases (e.g. pregnancy, renal failure)
- Concomitant therapies (e.g. oral anticoagulants)

Modified from Imazio M. Le Malattie del Pericardio, Pensiero Scientifico Editore 2016

**Figure 4.** Specific indications for low to moderate doses of corticosteroids as second level therapy in pericarditis (see text for comments).
Figure 5. Stepwise algorithm for treatment of pericarditis according to 5 levels. This algorithm is consistent with current European guidelines[3] and subsequent research on the topic.
Figure 6. Principal mechanisms of action of colchicine and anakinra. Colchicine blocks tubulin polymization interfering with neutrophils, where it is concentrated, moreover it is a non-specific inhibitor of the inflammasome (a cytoplasmatic complex of proteins assembled and activated by inflammatory states responsible for the activation of pro IL 1). Anakinra is an antagonist for IL 1β (the activated form of pro IL 1).
| **Infectious** | **Viral** (common): Enteroviruses, Herpesviruses (mainly EBV and CMV), Adenoviruses, Parvovirus B19 |
|---------------|----------------------------------------------------------------------------------------------------------------------------------|
|               | Bacterial: mainly *Mycobacterium Tuberculosis*, other bacterial agents less common |
|               | Fungal (very rare): Histoplasma spp (in immunocompetent patients), Aspergillus spp, Candida spp (in immunosuppressed patients) |
|               | Parasitic (Very rare): Echinococcus spp, Toxoplasma spp |
| **Non-infectious** | **Autoimmune** (*Systemic Inflammatory Diseases*: mainly LES, Rheumatoid Arthritis, Syogren Syndrome, Scleroderma, Vasculitis, mainly Behcet syndrome) |
|               | **Neoplastic** (Mainly secondary to lung cancer, breast cancer, lymphoma, leukemias, melanoma) |
|               | **Post-cardiac Injury Syndromes** (after acute myocardial infarction, PCI, Pacemaker, AICD implantation, ablation, cardiac or thoracic surgery) |
|               | Autoinflammatory Diseases (e.g. *Familial Mediterranean Fever*) |
|               | Metabolic (Renal Failure, Hypothyroidism) |
|               | Drug-related (rare): Lupus-like syndrome (e.g. procainamide, hydralazine, methyldopa, isoniazid, phenytoin) |
|               | Chemotherapy (e.g. Antracyclines) |
|               | Hypersensitivity with eosinophilia (e.g. penicilins, mesalazine, clozapine, vaccines) |

Main causes are reported in bold type.
Table 2. Main causes of pericarditis in unselected series with acute pericarditis.

|                  | Perm anyer-Miralda et al.\textsuperscript{7} | Zayas et al.\textsuperscript{8} | Reuter et al.\textsuperscript{9} | Imazio et al.\textsuperscript{10} | Gouriet et al.\textsuperscript{11} |
|------------------|---------------------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Patients         | 231                                         | 100                             | 233                             | 453                             | 933                             |
| Years            | 1977-1983                                   | 1991-1993                       | 1995-2001                       | 1996-2004                       | 2007-2012                       |
| Country          | Spain                                       | Spain                           | South Africa                    | Italy                           | France                          |
| Idiopathic       | 199 (86.0%)                                 | 78 (78.0%)                      | 32 (13.7%)                      | 377 (83.2%)                     | 516 (55.0%)                     |
| Autoimmune*      | 4 (1.7%)                                    | 3 (3.0%)                        | 12 (5.2%)                       | 33 (7.3%)                       | 197 (21.0%)                     |
| Neoplastic       | 13 (5.6%)                                   | 7 (7.0%)                        | 22 (9.4%)                       | 23 (5.1%)                       | 85 (8.9%)                       |
| Tuberculous      | 9 (3.9%)                                    | 4 (4.0%)                        | 161 (69.5%)                     | 17 (3.8%)                       | 4 (<1%)                         |
| Purulent         | 2 (0.9%)                                    | 1 (1.0%)                        | 5 (2.1%)                        | 3 (0.7%)                        | 29 (3.0%)                       |

*= includes systemic autoimmune, inflammatory diseases, and post-cardiac injury syndromes
| Setting     | Diagnostic Criteria                                                                                                                                 |
|-------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| Acute       | **CLINICAL CRITERIA:**  
with at least 2 of the 4 following criteria:  
1. pericarditic chest pain  
2. pericardial rubs  
3. new widespread ST-elevation or PR depression on ECG  
4. pericardial effusion (new or worsening)  
**Additional supporting findings:**  
**BIOMARKERS:**  
C-reactive protein, erythrocyte sedimentation rate, and white blood cell count);  
**IMAGING:**  
Evidence of pericardial inflammation by an imaging technique (CT, CMR). |
| Incessant   | Pericarditis lasting for >4–6 weeks but <3 months without remission.                                                                                  |
| Recurrent   | Episode of pericarditis with a symptom-free interval of 4–6 weeks or longer from previous attack of pericarditis.                                       |
| Chronic     | Pericarditis lasting for >3 months.                                                                                                                  |
Table 4. Common medical therapies for non-infectious pericarditis.

| Drug          | Mechanism of Action                            | Attack Daily Dose                  | Usual duration of attack dose* | LOE  |
|---------------|-----------------------------------------------|-----------------------------------|--------------------------------|------|
| Aspirin       | COX-inhibition                                | 750-1000mg TID                    | 1-2 weeks                      | B    |
| Ibuprofen     | COX-inhibition                                | 600-800mg TID                     | 1-2 weeks                      | B    |
| Indomethacin  | COX-inhibition                                | 25-50 mg TID                      | 1-2 weeks                      | B    |
| Colchicine    | Non specific inhibition of the inflammosome   | 0.5mg BID or 0.5mg if <70Kg       | 3 months (acute)               | A    |
|               |                                               |                                   | 6 months (recurrence)          |      |
| Corticosteroid| Mimic endogenous effects of cortisol          | 0.2-0.5 mg/kg of prednisone or equivalent | 2 weeks (acute)               |      |
|               |                                               |                                   | 4 weeks (recurrence)           |      |
| Azathioprine  | Blocking of purine and DNA synthesis          | Up to 2 mg/kg with slow increase  | At least 6 months              | C    |
| IVIG          | Modulation adaptative and innate immunity, clearance of infectious agents | 400-500mg/kg iv                  | 5 consecutive days, but they can be repeated after 1 month | C    |
| Anakinra      | Non selective inhibition of IL1α and IL1β     | 1-2 mg/kg (up to 100mg) sc        | 3-6 months                     | B    |

LOE= Level of Evidence: A- based on meta-analyses, >1 randomized controlled trial (RCT), B- single RCT, or observational non-randomized studies, C- case series, experts opinion. COX- Ciclooxygenase

*= for all treatments the attack dose is maintained till symptoms resolution and normalization of inflammatory markers (e.g. C-reactive protein) and other instrumental data (ECG, echocardiogram) then tapering is recommended by experts. This is especially important for corticosteroids where tapering is slow (e.g. to reduce the daily dose by 2.5 mg of prednisone or equivalent every 2 to 4 weeks according to the case).