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Contemporary diagnosis and treatment of recurrent pericarditis

Alessandro Andreis¹, Massimo Imazio¹, Gaetano Maria De Ferrari¹

1 University Cardiology, Cardiovascular and Thoracic Department, University of Torino, AOU Città della Salute e della Scienza di Torino, Torino, Italy

Corresponding author:

Massimo Imazio

University Cardiology, Cardiovascular and Thoracic Department, University of Torino, AOU Città della Salute e della Scienza di Torino, Corso Bramante 88, 10141 Torino, Italy

E-mail: massimo.imazio@unito.it

Abstract

Introduction: Acute pericarditis is frequently complicated with recurrences, which represent a diagnostic and therapeutic challenge for the physician, a bothersome trouble for patients. An incorrect treatment of pericarditis may cause further recurrence of symptoms, while an incorrect diagnosis may cause either a prolonged symptoms course with a possible risk of chronic constriction, or useless and potentially harmful treatments.

Areas covered: This review will focus on the most useful and recent diagnostic tools for recurrent pericarditis. Medline/Pubmed Library were screened with specific key search: "recurrent AND pericarditis". The research was restricted to papers published in the last 5 years (2015-2019) and papers in English language, in order to appraise the latest advances in diagnostic assessment.

Expert commentary

An accurate diagnosis of recurrent pericarditis is critical to provide timely and appropriate treatment of symptoms and prevention of further episodes. Diagnosis is made in case of recurrent symptoms associated with a documented evidence of pericardial inflammation. Further studies are needed to develop newer diagnostic tools aimed at identification of a predominant auto-inflammatory or auto-immune mechanism, which is essential to tailor the treatment.

Keywords (4-10): recurrent pericarditis; diagnosis; auto-inflammatory; auto-immune

Highlights:

- Acute pericarditis is frequently complicated with recurrences.
- A correct management of the first episode is critical for the prevention of recurrences.
- A typical diagnosis of recurrent pericarditis is made in case of symptoms relapse associated with a documented evidence of pericardial inflammation.
- An incorrect diagnosis of recurrent pericarditis may cause either a prolonged symptoms course with a possible risk of chronic constriction, or useless and potentially harmful treatments.
- Acute and recurrent pericarditis should always be treated according to evidence-based best clinical practice to prevent further symptoms occurrence.

1. Introduction

Acute pericarditis is frequently complicated with relapses, a diagnostic and therapeutic challenge for the physician, a bothersome trouble for the patient. This review will focus on the most complex diagnostic features as long as the most recent advances in the therapeutic management of recurrences.

1.1 Definitions

Acute pericarditis is a syndrome caused by pericardial inflammation, which may be primary or secondary to a concurrent active disease. According to 2015 ESC guidelines[1], it is diagnosed in the presence of at least 2 of the following features: pericardial chest pain (sharp, improved by sitting up and leaning forward), friction rub, ST-segment elevation or PR-segment depression on 12-lead ECG, new or worsening pericardial effusion detected by echocardiography.

Recurrent pericarditis occurs in case of one or more relapses after a documented first episode, with a minimum symptom-free interval of 4-6 weeks. When symptoms are persistent for more than 4-6 weeks or relapse before such interval, pericarditis course is defined as “incessant”. Pericarditis is defined as chronic when symptoms are persistent for more than 3 months[1].

2. Methods

Medline/Pubmed Library were screened with specific key search: “recurrent AND pericarditis”. The research was restricted to papers published in the last 5 years (2015-2019) and papers in English language. According to the research, 170 studies were initially screened. Among them, 122 studies were subsequently excluded by agreement between the authors (AA and MI) as non-pertinent for the present review, according to one or more of the following criteria: outdated results and concepts; redundant papers; non-relevant pre-clinical studies; non-pertinent case reports. Finally, 48 articles were selected in this systematic review and appraised as full text. Furthermore, the most relevant papers quoted in the aforementioned articles and in more recent guidelines on this topic were also included.

3. Recurrent pericarditis

3.1 Epidemiology and prognosis

Acute pericarditis is responsible for 5% Emergency Department admissions for non-ischemic chest pain[2]. Milder cases are usually managed in an outpatient setting, therefore the real incidence may be underestimated[3]. Prognosis is benign in high-income countries, where almost all cases are idiopathic and associated with a low risk of cardiac tamponade (3.2%)[4,5], chronic constriction (1.8%)[6] or in-hospital death (1.1%)[3]. A concurrent myocardial involvement occurs in 15% patients and does not affect negatively the prognosis[7]. Pericarditis occurs mostly in male subjects, especially between 16 and 65 years old[1], with a typical winter peak pattern for the first episode[8].

Recurrent pericarditis is the most common complication of acute pericarditis (Figure 1) and may occur in up to 30% patients after a first episode[9], rising to 50% in those who are not treated with colchicine ab initio, those who receive corticosteroids, those with multiple recurrences[10–12] or an unrecognised specific aetiology (especially bacterial or neoplastic)[11,12]. The risk of recurrence is influenced by the underlying etiology: indeed, patients with a non-idiopathic etiology (tuberculous, purulent, neoplastic, autoimmune) are at higher risk compared with idiopathic/viral (respectively 57% vs. 25% at 72 months)[6]. Despite the good prognosis, recurrent pericarditis has a negative impact on life quality [5,13]. About 5-10% patients with recurrences develop corticosteroid-dependent and colchicine-resistant recurrent pericarditis[14,15], when symptoms become refractory to traditional treatment and corticosteroids cannot be withdrawn (or reduced below a critical threshold).

Chronic corticosteroid treatment is associated with multiple harmful systemic side effects (osteoporosis, hypertension, diabetes, glaucoma, increased susceptibility to infections, muscle weakness, mood changes, weight gain, increased risk of gastrointestinal bleeding, Cushingoid syndrome)[16].

In the setting of acute pericarditis, a transient constriction due to active inflammation may be shown by diagnostic tests, revealing an increased pericardial stiffness. The risk of chronic constriction is increased according to specific etiologies (high risk in post cardiac injury syndromes -PCIS- and bacterial pericarditis, intermediate risk in immune or neoplastic pericarditis) and to clinical course: indeed, in case of incessant symptoms, progression to chronic constriction may occur rapidly, within few weeks/months. On the contrary, a direct evolution of idiopathic recurrent pericarditis to chronic constriction has never been reported in literature[13].

3.2 Etiology

The etiology of acute pericarditis is mostly idiopathic (>70% cases) in high-income countries, while infective etiologies (especially tuberculosis - TB) are predominant in low-income countries (70% cases)[17], and are associated with a worse prognosis. Tuberculous pericarditis implies a high mortality (25% at 6-months, rising to 40% in patients with associated HIV infection)[18,19]. Non-infective causes include PCIS (6-21%), autoimmune and autoinflammatory diseases (2-24%), cancer (5-9%, especially lung, breast, leukemias and lymphomas), connective tissue diseases (such as rheumatoid arthritis, Sjogren syndrome, lupus erythematosus, 2-7%)[20].

Although recurrent pericarditis is frequently classified as idiopathic or viral (new infection, re-infection, chronic viral infection or reactivation of a previous viral infection)[11–13,21], it is likely that many cases are consequence of an inadequate anti-inflammatory treatment (drug choice, doses, treatment duration, tapering) or inobservance of physical restriction during the previous episode[22,23] (Figure 2).

3.3 Pathogenesis

During the first episode of acute pericarditis, in predisposed patients environmental factors (such as viral/bacterial infection, cardiac injury, etc.) may trigger auto-reactive processes able to establish and sustain a chronic low-grade inflammation over time [14]. A predominantly auto-immune or auto-inflammatory mechanism is believed to be responsible for subsequent pericarditis recurrences.

An autoimmune mechanism is suggested by the finding of auto-antibodies in the serum of patients with recurrent pericarditis: heart-specific autoantibodies (such as anti-heart and anti-intercalated disks) were found in 68% patients[24,25] and anti-nuclear antibodies in 45%[26]. Furthermore, proinflammatory cytokines (interferon- γ , IL-6, IL-8) were found in the pericardial fluid but not in the serum of patients with relapsing pericarditis, suggesting a local inflammation[25]. The usually good clinical response to immunosuppressive drugs further support this mechanism. The reason for inappropriate adaptive immune response may be due to a concurrent auto-immune systemic disease, cross-reactivity triggered by infection or myocardial injury with auto-antigens exposure[27].

An autoinflammatory mechanism is suggested by the several similarities between idiopathic recurrent pericarditis and rare autoinflammatory diseases such as tumor necrosis factor receptor-associated periodic syndrome (TRAPS), Familial Mediterranean Fever (FMF) and Still's disease. Those diseases are typically characterized by recurrent fever and CRP elevation. Furthermore, up to one third cases of FMF and TRAPS are complicated with pericardial involvement, which may evolve into recurrent pericarditis. The inflammatory response underlying pericarditis flares is triggered by NLRP3 inflammasome, which is hyper-activated in FMF and TRAPS. Its activation causes an over-production of interleukin-

1 (IL-1), which amplifies the inflammatory cascade, recruiting neutrophils and macrophages at the site of injury. A gain-of-function mutation of the MEFV gene is present in FMF, while a gain-of function mutation of the TNFRSF1A gene is present in TRAPS, both of them triggering NLRP3 activation with IL-1 released downstream[28,29]. Recurrent pericarditis may occur in patients with Still's disease, whose autoinflammatory pathogenesis and clinical course mimics TRAPS [30].

The auto-inflammatory response is mainly based on IL-1 overproduction, while auto-immune response is mostly based on the signaling pathway triggered by type I interferon. The first type of response is probably predominant in patients with idiopathic recurrent pericarditis and in those presenting with fever and CRP elevation, while the second one is probably predominant in patients with a concurrent autoimmune systemic disease[14].

3.4 Clinical manifestation

Recurrences occur with signs and symptoms similar to the first episode, even though usually progressively milder through subsequent relapses[13]. Typical pericardial chest pain (sharp, improved by sitting up and leaning forward), similar to previous episodes, is reported by 95-100% patients with recurrences. Friction rub may be heard in 20-37% patients, ECG abnormalities can be found in 60-74%, while pericardial effusion in 56-64%. Cardiac tamponade is a rare presentation of recurrent pericarditis (0-2%)[10–12].

3.5 Diagnosis of recurrent pericarditis

According to current ESC guidelines[1], diagnosis of recurrent pericarditis is made in case of: a previous documented episode of acute pericarditis; a symptom-free interval of 4-6 weeks; recurrent pericardial chest pain associated with at least one of the subsequent features: friction rub, ST-segment elevation or PR-segment depression on 12-lead ECG, new or worsening pericardial effusion, increased levels of serum inflammation markers (C-Reactive Protein, erythrocyte sedimentation rate, white-cell count). The 4-6 weeks interval was arbitrarily stated, based on the usual duration of anti-inflammatory drugs tapering[13]. C-reactive protein may be negative in up to 22% patients, especially in case of early presentation within 12-24h from symptoms onset. For this reason, serial testing is recommended in case of high clinical suspicion[31]. The major differential diagnoses to be ruled out include acute coronary syndromes, early repolarization and restrictive cardiomyopathy [1].

A consensus document issued in 2013 by the American Society of Echocardiography proposed the evaluation of ancillary supportive data (such as fever, CRP and troponin levels), and the use of second-level imaging techniques, such as computed tomography (CT) and cardiac magnetic resonance (CMR) to assess doubtful cases[32–34].

CMR can assess the presence (and extent) of pericardial inflammation[35]. Late gadolinium enhancement (LGE) reflects increased vascularity[36], while pericardial edema appears bright on short-tau inversion-recovery time (STIR)-T2-weighted images[37]. CMR allows detection of pericardial thickening, which is a sign of inflammation. Pericardial LGE quantification has a prognostic role: increased LGE has been associated with a shorter time to relapse and a higher 6-months recurrence rate[38]. In the setting of constrictive pericarditis, quantitative LGE was used to predict the possibility of improvement with anti-inflammatory treatment[37]. CMR can also be used to tailor therapy[39]. In a retrospective study on 507 patients, those undergoing a CMR-guided therapy received a lower total dose of prednisone, had a lower mean glycosylated hemoglobin and a lower number of recurrences (1.2 vs. 3.6)[40].

CT can assess pericardial inflammation by contrast-enhancement[41,42], pericardial thickening (supportive feature for acute pericarditis)[43] and also characterization of pericardial effusion, based on attenuation values (<10 Hounsfield Unit indicates a

transudate; 20-60 indicates exudate; >60 indicates haemorrhagic pericardial effusion)[44]. Moreover, CT can accurately assess the location and extent of pericardial calcifications in calcific constrictive pericarditis[45]. Epicardial fat volume determined with CT was lower in patients with a secondary cause of pericarditis, with poor response to NSAIDs and with more severe disease course (development of recurrent, incessant or constrictive, pericarditis and/or need for treatment up-titration)[46]. A recent study tested the usefulness of [18F]-2-deoxy-2-fluoro-d-glucose (FDG) Positron Emission Tomography/Computed Tomography (PET/CT), showing that increased pericardial uptake is associated with a higher risk for relapse in acute pericarditis with pericardial effusion[47].

Recurrent pericardial chest pain without evidence of pericardial inflammation occurs in 10% patients, as demonstrated in 2004 in a cohort of 275 consecutive patients. These patients should be given analgesics (i.e. acetaminophen), avoiding corticosteroids, and should be re-evaluated more frequently because of an increased risk of subsequent clinically manifest recurrences (33% vs. 15% at 40 months)[48]. Previous corticosteroid use (OR=5.2, 95% CI 2.2-12.3), female gender (OR=4.3, 95% CI 1.8-0.6) and previous recurrences (OR=3.7, 95% CI 1.3-10.2) are risk factors associated with this syndrome.

In patients with multiple periodic recurrences, an autoinflammatory disease (TRAPS, FMF, Still's disease) should be ruled out. In a study published in 2012 by Cantarini et al.[49], 6% patients with idiopathic recurrent pericarditis were carriers of TNFRSF1A gene mutation. This mutation should be suspected especially in patients with a positive family history for recurrent pericarditis or periodic fever syndromes, with a poor response to colchicine, with recurrences after the first year from the index attack or in those treated with immunosuppressive drugs.

High fever, subacute onset, severe pericardial effusion, cardiac tamponade, incomplete symptoms resolution with anti-inflammatory drugs identify patients with poorer prognosis, with high probability of non-idiopathic cause. In these patients hospitalization and etiologic search should be considered[17]. When a specific etiologic agent is not identified by the initial diagnostic work-up in immunocompetent patients, it portends a good prognosis and usually it is not required further investigation since the precise diagnosis is usually irrelevant for the clinical management[42,50]. Pericardiocentesis with fluid analysis should not be routinely performed, since even when a specific viral etiology is found, it would not change the clinical approach in an immunocompetent patient. Indeed, uncomplicated cases usually have idiopathic or viral etiology. In 2013, Pankuweit et al. demonstrated that a significant proportion of pericardial effusions were due to Parvovirus B19 or Epstein Barr Virus infection, in a cohort of 259 patients undergoing pericardiocentesis[51].

Among patients with corticosteroid-dependent and colchicine-resistant recurrent pericarditis, a further diagnostic assessment should be targeted in order to rule out latent TB, HIV or HBV/HCV infections and underlying systemic autoinflammatory or autoimmune diseases[52].

Despite rare in middle- or high- income countries, tuberculous pericarditis should always be excluded, most of all in patients with suspect signs and symptoms. Chest X-ray and interferon gamma releasing test (or alternatively tuberculin skin test) should be performed to rule out latent TB in asymptomatic patients. If suspect lung infiltrates are shown by chest X-ray and the patient report suspect symptoms, bronchoscopy with bacterioscopy, genetic tests and bronchial washings culture should be performed. In case of high clinical suspicion of tuberculous pericarditis, pericardiocentesis with pericardial biopsy may be considered to obtain a certain diagnosis [53].

3.6 Treatment

Anti-inflammatory treatment (Table 1), using aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) in association with colchicine, is the first-choice treatment for first and

subsequent pericarditis episodes[1]. In the event of a non-idiopathic etiology, specific causal treatment should be the therapy mainstay, associated with anti-inflammatory treatment for symptoms control[1]. Exercise restriction is critical and should always be recommended. Treatment should be continued until complete symptoms resolution, normalization of serum inflammation markers, echocardiography and ECG[54]. A proper treatment of pericarditis is of paramount importance to avoid subsequent recurrences (Figure 2).

Corticosteroids may be considered in specific contexts, such as connective tissue diseases, renal failure, pregnancy, oral anticoagulants[55]. They are the second- and third-choice treatment in case of contraindications or inefficacy of colchicine and aspirin/NSAIDs[56]. Although allowing a prompt remission of symptoms, corticosteroids have been associated with an increased risk of subsequent relapses (RR=2.89, 95% CI 1.10-8.26)[10]. Lower doses of corticosteroids are preferred (such as prednisone 0.2-0.5 mg/kg daily) since higher doses (prednisone 1 mg/kg/die or greater) are associated with even greater risk of recurrences (65% vs. 33%), in addition to systemic side effects (osteoporosis and Cushingoid syndrome)[16]. A careful clinical and laboratory testing monitoring should be performed in patients on corticosteroids, and they should be offered appropriate calcium and vitamin D supplementation.

Colchicine should always be added to aspirin or NSAIDs, not only in the first episode, as demonstrated in the COPE trial and ICAP trial[57,58], but also in recurrences[59]. Colchicine not only inhibits neutrophils but also NLRP3 inflammasome, caspase-1 (activator of IL-1) and TNF α [14]. The CORE trial demonstrated that colchicine associated with NSAIDs reduced symptom persistence at 72h (10% vs. 31% in control group) and subsequent recurrences (24% vs. 51%) in patients with a first recurrence of pericarditis[10]. Similar results were observed in the subsequent CORP trial[11]. A more recent trial, the CORP-2, found that colchicine was also useful in patients with multiple documented relapses: on top of conventional treatment, colchicine allowed a reduced symptom persistence at 72h (19% vs. 44%) and subsequent recurrences (22% vs. 43%)[12]. The number of patients needed to treat (NNT) to prevent one recurrence was 9 in the ICAP trial, 5 in the CORP-2. Colchicine should be continued for at least 6 months in recurrent pericarditis, while corticosteroids tapering should be started as soon as symptoms are controlled and serum inflammation markers are normalized. In case of symptoms relapse during corticosteroids tapering, dosage should not be increased again and symptoms should be treated with NSAIDs and colchicine[60].

In the setting of corticosteroid-dependent and colchicine-resistant recurrent pericarditis, “steroid-sparing” fourth-line treatments should be considered, including immunosuppressive drugs (azathioprine, i.v. immunoglobulin therapy) and recently studied anti IL-1 drugs (anakinra)[61].

Azathioprine is an immunosuppressive agent inhibiting lymphocyte generation. In a study on 46 patients, azathioprine allowed corticosteroid withdrawal in 85% patients after one year of treatment[62]. Its efficacy is more evident in the long term and less valuable in the acute setting. Iv immunoglobulins are useful, especially in case of concurrent systemic autoimmune disease, although they require hospitalization for administration, besides experience in literature is limited (30 cases reported)[55,63].

Anti-IL-1 agents, such as anakinra, target the critical element of the inflammatory cascade. Despite limited experience reported in literature (some case reports[64–77], a few case series[78–81] and one randomized and controlled trial on 21 patients[82]), its role as immuno-modulator may successfully reduce pericarditis recurrences. The AIRTRIP trial[82] showed a reduced incidence rate of 0.11 / year-patient (vs. 2.06 / year-patient in placebo group) in the setting of corticosteroid-dependent and colchicine-resistant recurrent pericarditis. Anakinra allowed a rapid remission of symptoms (within 8 days) and CRP normalization in addition to corticosteroids withdrawal in all 21 patients.

Fifth-line treatment is represented by pericardiectomy, which is associated with a 5-10% mortality. Prognosis is worse in case of advanced age, non-radical pericardiectomy, radiation or PCIS etiology [83]. A suggested algorithm for pericarditis treatment is shown in Figure 3.

4. Conclusions

An accurate diagnosis of recurrent pericarditis is critical to provide timely and appropriate treatment of symptoms and prevention of further episodes. Certain diagnosis is made in case of recurrent symptoms associated with a documented evidence of pericardial inflammation. Further studies are needed to develop newer diagnostic tools aimed at identification of the predominant mechanism underlying recurrences (i.e. auto-inflammatory or auto-immune), which is essential in order to tailor the treatment.

Expert opinion

Recurrent pericarditis is the most common adverse event subsequent to a first episode of acute pericarditis. Many studies have recently provided insights not only in the pathophysiology of recurrent pericarditis but also in the diagnostic and therapeutic management of patients.

A correct management of the first episode of pericarditis is critical for preventing recurrences. The lack of concurrent therapy with colchicine at the first episode, the early and unjustified use of corticosteroids (especially at higher doses), the under dosage (or wrong daily distribution) of anti-inflammatory drugs, the early or rapid withdrawal of drugs, the practice of physical exercise, are some of the most common causes of recurrent or persistent pericarditis. Corticosteroid-dependent, colchicine-resistant idiopathic recurrent pericarditis has a benign prognosis, though bothersome for patients and challenging for clinicians. Actually, only patients with specific etiologies (i.e. bacterial, PCIS) and/or persistent symptoms have a high risk of evolution to chronic constriction, opposed to patients with idiopathic recurrent pericarditis in whom this complication has never been reported.

For such reasons, acute pericarditis should always be treated according to evidence-based best clinical practice to prevent further symptoms occurrence. In the same way, an incorrect diagnosis of recurrent pericarditis may cause either a prolonged persistent course of symptoms (with the aforementioned risks) or useless and potentially harmful treatments (such as corticosteroids).

The mainstay of the diagnosis of recurrent pericarditis is purely clinical and based on accurate medical history and symptoms evaluation (Figure 4). Relapsing chest pain with similar characteristics to previous symptoms alone is insufficient for the diagnosis of recurrent pericarditis, which should always be made according to recommended criteria. Indeed, chest pain should be associated with at least one documented sign of pericardial inflammation (pericardial rubs, ECG alterations, new or worsening pericardial effusion or increased levels of serum inflammation markers).

In addition to the aforementioned traditional signs, second-level imaging techniques, such as CMR and CT, have shown remarkable diagnostic accuracy in the recent few years. Among patients with uncertain recurrence of pericarditis, CMR or CT may be useful to rule-out pericardial inflammation. In patients with diagnosis of recurrent pericarditis, such tools may be helpful to tailor therapy. Second-level imaging may reveal signs of "active" inflammation, identifying patients in whom pericardial constriction might revert with anti-inflammatory treatment.

When the diagnosis of recurrent pericarditis is established, further etiologic research should be performed, according to epidemiology and clinical suspect. A latent viral or tuberculous infection should always be excluded (through specific lab tests, chest-X ray and

pericardiocentesis with biopsy in selected cases), as well as possible concurrent unknown cancer (organ-focused CT or total-body CT), autoimmune systemic disease (Lab tests, medical history, physical exam, additional tests), autoinflammatory disease (medical history, genetic testing, additional tests). When a secondary cause of pericarditis is identified, specific causal treatment is the mainstay of therapy, while anti-inflammatory drugs should be associated for symptoms control.

In the setting of corticosteroid-dependent, colchicine-resistant recurrent pericarditis, the identification of a predominantly auto-inflammatory or auto-immune pathogenesis is important and should be guided by clinical assessment and diagnostic tests. Indeed, a clinical presentation with a classical inflammatory phenotype (recurrent pericarditis associated with fever and CRP elevation) is a strong clue for auto-inflammatory mechanism. In these patients, anti-IL 1 drugs, such as anakinra, should be offered early. In the absence of a classical inflammatory mechanism, immunosuppressive drugs (azathioprine) or intravenous immunoglobulins might be offered.

Further studies should be aimed at the identification of diagnostic tools capable of discriminating the predominant mechanism underlying recurrent pericarditis (auto-immune or auto-inflammatory), helping the clinician to tailor therapy.

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* of interest

** of considerable interest

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Figure Legends

Figure 1 – Complications rates in acute idiopathic pericarditis

Figure 2 – The five golden “D” to prevent recurrent pericarditis

Figure 3 – Suggested treatment levels for recurrent pericarditis

Figure 4 – Suggested flow-chart for pericarditis diagnosis and treatment

Tables

Table 1 – Treatments for recurrent pericarditis

	Attack Dose	Duration	Suggested tapering protocol ***
Aspirin*	Acetylsalicylic acid 750-1000 mg every 8 hours	1-2 weeks	Decrease doses by 250 mg every 10 days (stop after 4 weeks).
NSAIDs*	Ibuprofen 600-800 mg every 8 hours	1-2 weeks	Decrease doses by 200 mg every 10 days (stop after 4 weeks).
	Indomethacin 25-50 mg every 8 hours		Decrease doses by 25 mg every 10 days (stop after 4 weeks).
Colchicine	0.5 mg once daily (if <70 kg or renal failure with GFR 35-60 ml/min), 0.5 mg twice daily (if >70 kg).	6-12 months (recurrent)	Not required; alternatively, decrease to 0.5 mg every other day (if <70 kg) or 0.5 mg once daily (if >70 kg) for a few weeks
Corticosteroids**	Prednisone 0.2-0.5 mg/kg daily	As soon as complete resolution of symptoms and normalization of markers of serum inflammation have been obtained	>50 mg daily: decrease doses by 10 mg/day every week. 25-50 mg daily: decrease doses by 5 mg/day every week 15-25 mg daily: decrease doses by 2.5 mg/day every 1-2 weeks <15 mg daily: decrease doses by 2.5 mg/day every 2 weeks
Azathioprine	1 mg/kg daily (starting dose), then progressively increase to 2-3 mg/kg daily (maximum dose of 150 mg/daily)	several months	several months
Intravenous immunoglobulins	400-500 mg/kg/ daily	5 days (may be repeated after one month)	Not required
Anakinra	1-2 mg/kg daily (maximum 100 mg/day)	several months	unknown

*Association of a proton-pump inhibitor is suggested

**Calcium supplements (1200-1500 mg/day) and Vitamin D supplements (800-1000 IU/day) are suggested

*** Protocol may be prolonged in patients with multiple previous recurrences