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Management of pericarditis

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ABSTRACT

Pericarditis is an inflammatory syndrome involving pericardium, which is a double-walled sac consisting of two leaves, a serous visceral layer in contact with the myocardium (pericardium) and a parietal fibrous one, delimiting a cavity (pericardial cavity) containing pericardial fluid. Pericarditis may occur isolated or as a manifestation of a systemic disorder. Diagnosis and correct management of pericarditis can be difficult and its natural history is often characterized by a lot of relapses. Treatment of acute pericarditis should target the underlying etiology. The diagnosis is based on characteristic clinical findings, electrocardiogram, and echocardiography. The goals of treatment are relief of pain, resolution of inflammation (and, if present, pericardial effusion), and prevention of recurrence. Despite a significant impairment of the quality of life, pericarditis usually has good long-term outcomes.

Definition

Pericardial syndrome can present clinically as pericarditis, pericardial effusion, cardiac tamponade, and constrictive pericarditis. The last three entities may occur without pericarditis. A particular clinical form is myopericarditis. Pericarditis is an inflammatory syndrome involving pericardium, which is a double-walled sac consisting of two layers, a serous visceral layer in contact with the myocardium (pericardium) and a parietal fibrous one, delimiting a cavity (pericardial cavity) containing pericardial fluid.[1] Pericarditis may occur isolated or as a manifestation of a systemic disorder.[2]

Pericarditis is defined as: i) acute, which indicates a new onset of inflammatory syndrome with or without new pericardial effusion; ii) incessant, if the symptoms last for > 4-6 weeks; iii) chronic, if the symptoms last for >3 months; iv) constrictive, which is characterized by impaired diastolic filling of the ventricles due to pericardial disease. This condition results from a fibrinous or acute serous-fibrinous pericarditis or by the reabsorption of a chronic pericardial effusion; the consequence is the obliteration of pericardial cavity leading the modification of the pericardium into a scarred and inelastic tissue, interfering with ventricular filling.[3]

Pericardial effusion is an abnormal accumulation of fluid in the pericardial cavity caused by an increased production or by a decreased absorption of the fluid, due to a general increase in systemic venous pressure as a result of congestive heart failure or pulmonary hypertension.

Pericardial effusion may be classified according to its onset (acute or subacute *vs*. chronic when lasting >3 months), distribution (circumferential or loculated), hemodynamic impact (none, cardiac tamponade, effusive-constrictive), and composition (exudate, transudate, blood, rarely air, or gas from bacterial infections).

Cardiac tamponade is an acute or chronic compression of the heart due to the accumulation of pericardial fluid, pus, blood, clots or gas, as a result of inflammation, trauma, rupture of the heart or aortic dissection.

Myopericarditis is defined by the concomitant myocardial involvement.[1]

Etiology

The 2015 ESC guidelines[1] propose an etiological classification of pericardial diseases, including infectious and non-infectious causes. The etiology is influ-

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enced by epidemiological background, patient populations, and clinical setting.

In developed countries, viruses are the most common causes, while tuberculosis (TB) is the most common cause in the world and in developing countries, where it is often associated with human immunodeficiency virus (HIV) infection.[1]

Recurrent pericarditis is sometimes caused by inadequate treatment of the first episode of pericarditis.[1]

In developed countries, recurrent pericarditis is idiopathic in most immunocompetent patients, but it is thought to have an immune-mediated or autoinflammatory etiology,[1,4-7] with a pivotal pathogenetic role of interleukin (IL)-1. An immune-mediated etiology is also suspected in relapsing pericarditis that occurs in postpericardiotomy syndrome.[4-6] Laboratory tests conducted on pericardial fluid and tissue detected a viral etiology in 20% of cases.[1]

There are few clinical data on myopericarditis etiology; however, they suggest that viral infections are the most common causes in developed countries.

In developed countries the most common causes of constrictive pericarditis are idiopathic or viral (42-49%). Other causes are: post-cardiac surgery (11-37%), post-radiation therapy (9-31%, especially for Hodgkin's disease or breast cancer), post-myocardial infarction effusion, post-traumatic pericarditis, connective tissue disorders such as systemic lupus erythematosus and rheumatoid arthritis (3-7%), post infectious causes (tuberculosis or purulent pericarditis 3-6%) and other rare causes (malignant tumors especially breast and lung cancer and lymphomas, drug-related, asbestosis, sarcoidosis; uremic pericarditis. 10% of all causes overall). In developing countries, constrictive pericarditis has a higher prevalence and tuberculosis is the major etiological agent. This cause is increasing among immigrant patients from developing countries and HIV patients.[1,3,8]

Pericardial effusion is often idiopathic in outpatient population, whereas in inpatients the most common causes are neoplastic pericarditis, uremic pericarditis and iatrogenic causes.[1]

Risk factors and pathophysiology

The incidence of acute pericarditis is two times higher in men than in women.[1,9,10] Experimental viral studies on myocardial inflammation have suggested a role of sex hormones. The incidence of acute pericarditis in men decreases with age, after adolescence, but shows an increase after 45 years of age, which suggests a non-linear relationship with testosterone. Progesterone predisposes to cardiac inflammation, while estrogen inhibits it, favoring proinflammatory T-cell inhibition, stimulating T-cell inhibitors and favoring a Th2-type immune response.[10]

Postpericardiotomy syndrome is thought to be the result of a hypersensitivity reaction to antigens or molecules such as damage-associated molecular patterns (DAMPs) that activate toll-like receptor or nod-like receptor. DAMPs originate from injured myocardium and/or pericardial tissue. Anti-fibrillary or anti-sarcolemmal autoantibodies have been detected in the blood, but their role remains to be defined. Viral infections can also be implicated in the pathogenesis of this syndrome.[3]

The most common pathophysiology of myopericarditis is based on the inflammation of myocardium and pericardium by direct cytolytic or cytotoxic mechanism and/or with subsequent immune-mediated mechanism after viral infection. These mechanisms are related to connective tissue diseases, intestinal chronic inflammatory diseases, and radiation-induced, drug-induced or vaccine-associated myopericarditis.[1] In patients with autoimmune disease and myopericarditis, a high titer of anti-heart autoantibodies and anti-intercalated disk autoantibodies is detected by indirect immunofluorescence, which represents autoimmune markers in patients with myocarditis documented with biopsy, dilated cardiomyopathy and related pathologies.[4]

Relapsing pericarditis occurs from 15 to 30% of cases, and may increase up to 50% after a first relapse in patients who are not treated with colchicine (especially if treated with corticosteroids).[1]

Recurrent pericarditis is frequently idiopathic and it was thought to have an immunologic or autoinflammatory pathogenesis. Recurrences are sometimes heralded by repeated viral infections, but they often occur due to rapid tapering of drugs, particularly corticosteroids, or to the fact that non-steroidal anti-inflammatory drugs (NSAIDs) are used at low doses, or given only orally and not intravenously in hospitalized patients.[7] Other cases of recurrences have been described in patients with a predisposing genetic background. Possible non-invasive clues for autoimmunity are antinuclear antibodies (ANA, 43% of adults, at low titer),[11] dry eyes, arthralgias, and a subacute course. Conversely, clues for an autoinflammatory pathogenesis are acute attacks followed by complete resolution, strikingly elevated C-reactive protein (CRP), high fever, and pleuro-pulmonary and systemic involvement; generally, in these patients autoantibodies cannot be detected and familiar occurrence has been reported in 10% of the cases.

Such phenotype looks strikingly similar to those observed in some autoinflammatory diseases, such as familial Mediterranean fever, or tumor necrosis factor receptor-associated periodic syndrome, conditions where the inflammasome and IL-1 play a pivotal role. Typical mutations of these entities are however rare in recurrent pericarditis, but new and still unknown mutations may be present. These patients may have a diathesis related to the presence of genes encoding proteins involved in activation/regulation of inflammatory path-

ways; this diathesis may induce an exuberant autoinflammatory response, initiated non-specifically by many different stimuli: virus, bacteria, trauma, minor intrapericardial bleeding (often iatrogenic), surgery, tissue necrosis, pleural or peritoneal inflammation, excessive cold, finally activating the inflammasomes.[7]

Considering the dramatic response to anti-IL-1, for this disease, the term idiopathic seems somehow inappropriate for a condition that responds dramatically to mono-therapy with anti-IL-1 agents.[5,6,12,13] The pathogenesis of recurrent acute pericarditis in a proportion of patients is comparable to most other inflammatory diseases, and we may consider abandoning the term idiopathic in this setting. Acceptable terms might be *autoinflammatory pericarditis* for the typical phenotype previously described, or *autoimmune pericarditis*, for those cases without *autoinflammatory* features and with positive autoimmune serology (*e.g.* organ-specific anti-heart or non-organ-specific autoantibodies).

Diagnosis

The diagnosis is essentially clinical, based on the presence of at least two of the following criteria:[1] typical chest pain, pericardial friction rub, typical electrocardiogram (ECG) changes, new or worsening pericardial effusion. Acute pericarditis is usually suspected based on a history of typical chest pain, persistent fever and a pericardial effusion.[14] Chest pain is typically sharp and pleuritic, fairly sudden in onset and occurs over the anterior chest, improved by sitting up and leaning forward. We see it in about 95% of cases.[15] A specific sign for pericarditis is the radiation of chest pain to the trapezius ridge. Patients with uremic pericarditis or pericarditis associated with a rheumatologic disorder may not report chest pain. Pericardial friction rub may be present as a superficial scratchy or squeaking sound heard over the left and/or right sternal border. It can be heard better using the diaphragm of the stethoscope. Additional testing such as blood tests, chest radiography, electrocardiography and echocardiography confirm the diagnosis. Patients with an infectious etiology may present with signs and symptoms of sepsis. The ECG is usually helpful in the evaluation of patients with suspected acute pericarditis. It typically evolves through four stages[16] which include: i) Stage 1 (in the first hours to days): diffuse ST elevation concave up with reciprocal ST depression in leads aVR and V1 with depression of the PR segment in the other limb leads and in the left chest leads, primarily V5 and V6. Thus, the PR and ST segments typically change in opposite directions;[15] ii) Stage 2 (in the first week): normalization of the ST and PR segments; iii) Stage 3 (duration is not well-documented and likely highly variable): development of diffuse T-wave inversions, generally after the ST segments have become isoelectric; iv) Stage 4: normalization of the ECG.

The duration of the ECG changes in pericarditis generally depends on its cause and on the extent of the associated myocardial damage.[17] Arrhythmias are not common in acute pericarditis, except in surgical setting,[18] but atrial fibrillation may occur in 4.3% of cases of acute pericarditis. Atrial or ventricular arrhythmias are suggestive of concomitant myocarditis or of an unknown prior cardiac disease. Sinus tachycardia is also quite common.[19]

Complete blood count, troponin level, erythrocyte sedimentation rate, and serum CRP level support the diagnosis. Viral serology and virus genomes are not routinely indicated.[20] ANA can be useful in selected cases (*e.g.*, young women, in case of polyserositis), but they are not specific tests. The interferon-gamma release assay (quantiferon TB assay) may be more helpful in immunocompromised or HIV positive patients and in areas where tuberculosis is endemic.

Cardiac magnetic resonance with administration of gadolinium or computed tomography imaging might be done in selected patients (*e.g.*, suspected constrictive pericarditis, complicated course, suspicion of specific etiology, particularly neoplasms, concomitant pleuropulmonary diseases and lymphadenopathies, *etc.*).[21,22]

Pericardiocentesis with bacterial cultures and/or cytological exam should be considered in patients with suspect bacterial or malignant etiology, or in patients with a symptomatic effusion refractory to medical therapy, but the diagnostic yield is low.[23]

Generally, indication to pericardial biopsy is restricted to patients with recurrent pericardial effusions and cardiac tamponade after prior pericardiocentesis (therapeutic biopsy).[12,22]

Echocardiography in pericardial diseases

Echocardiography is the technique of choice for the diagnosis of pericardial effusion; it can be evaluated by M-mode, two-dimensional (2D) and three-dimensional (3D) echocardiography.

On M-mode and 2D echocardiography, pericardial effusion appears as an echo-free space between the two-pericardial layers, in localized areas, or around the heart. When the volume of fluid is small, it can be seen as a black echo-free space present only posterior to the heart in the parasternal short and long axis view, and may be present only in the systolic phase. When the volume of fluid is more than 25 mL, an echo free space may be seen all around the heart throughout the cardiac cycle. When the amount of fluid is massive, the heart may have a swinging motion in the pericardial cavity.

Measurements of fluid thickness are acquired in the diastolic phase, anteriorly and posteriorly on the PLAX or SAX views, apically in the A4C, A3C or A2C views and inferiorly in the subcostal view. Fluid adjacent to the right atrium is an early sign of pericardial effusion.

Differentiation between pericardial and pleural effusion is an important point. Pericardial effusion is usually located circumferentially. If the echo free space is present only anteriorly, it is more likely to be due to the presence of epicardial fat or a pleural effusion. A pericardial effusion is anterior to the descending thoracic aorta in PLAX view whereas a pleural effusion is posterior to it. A pericardial effusion is rarely >4 cm thick. If pericardial and pleural effusions co-exist, then a linear echo (the pericardium) separates them. A pleural effusion on the left side allows cardiac imaging from the back. An echocardiographic pitfall may be the differentiation between pericardial effusion and pericardial fat. Epicardial fat tissue is more prominent anteriorly but it may appear circumferentially, thus mimicking an effusion. Fat is slightly echogenic and moves in concert with the heart, two characteristics that help to differentiate it from an effusion which is echolucent and motionless. Isolated anterior echo (under the right ventricle) free space may be due to mediastinal fat or fibrosis. This condition does not have any pathological consequences, and it can be differentiated from effusion because of its higher density. Based on a simple semi-quantitative echocardiographic assessment of the largest end-diastolic echo-free space, we can distinguish a pericardial effusion as: i) mild (<10 mm); ii) moderate (10-20 mm); iii) large (>20 mm).

There is no precise quantification of the absolute volume of pericardial fluid, but a circumferential echo-free space smaller than 0.5 cm may correspond to a volume of fluid <100 mL, a circumferential echo-free space of approximately 1 cm may correspond to a volume of 100-500 mL, and a circumferential echo-free space >1 cm may correspond to a volume of pericardial fluid >500 mL.

The physiological consequences of pericardial effusion depend on the following factors: i) amount of effusion; ii) rate of fluid accumulation. A slowly expanding pericardial effusion can become severe (>1000 mL) with little increase in pericardial pressure, and without important hemodynamic consequences. Rapid accumulation of even a small volume of fluid (50-100 mL) can lead to a marked increase in intrapericardial pressure, with subsequent compression of cardiac chambers.

The echocardiographic signs of tamponade can be found in: i) 2-D echo and M-mode; and ii) Doppler.

2-D echo and M-mode

- *Diastolic right ventricular collapse*: this occurs when intra-pericardial pressure exceeds intraventricular pressure and occurs in early diastole. This can be observed in PLAX and A4C views, but being a rapid movement, it may need to be resolved with M-mode through the right ventricular outflow tract (RVOT) or RV free wall in a PLAX view. The RVOT has the higher compliance and it is the first part of the RV to collapse. When the entire body of the RV collapses, it is an indicator of a more substantial elevation in intra-pericardial pressure. Although this sign is a relatively sensitive and specific marker for tamponade, RV diastolic collapse is sensitive to alterations in ventricular loading conditions and may not be seen in the presence of right ventricular hypertrophy.
- *Right atrial collapse*: Raised intra-pericardial pressure causes right atrium collapse even after atrial systole. Atrial collapse is therefore a late diastole, early systole phenomenon. With increasing intrapericardial pressures, the atrium remains collapsed throughout diastole as well and buckles inward, reversing the normal wall curvature. While this is better seen in the A4C and subcostal views, M-mode through the RA wall may be necessary to clearly identify the collapse, particularly when heart rate is high. Right atrial collapse is virtually 100% sensitive for tamponade but not specific. Duration of this collapse exceeding one third of the cardiac cycle increases specificity without sacrificing sensitivity. Left atrial collapse is seen in about 25% of patients and it is very specific for tamponade.
- *Inferior vena cava* (IVC) plethora with a lack of change with breathing is clinically relevant: because of the elevated filling pressures of right heart, the IVC becomes distended (>2 cm diameter) and has less than 12% variation in diameter with respiration.

Doppler

- Exaggerated respiratory variation in tricuspid and mitral inflows.
- *Increased left ventricular outflow tract velocity time integral (LVOT VTI) variation*: marked variations with respiration (>25%) in mitral and tricuspid inflow velocities as well as LVOT and RVOT VTIs are commonly seen. These changes may not be evident in the presence of a hypertrophic right ventricle as seen in pulmonary hypertension, thickening of ventricular walls due to malignancy, overlying inflammatory response or overlying thrombus and in severe hypovolemia - the so-called low-pressure cardiac tamponade.[24-28]

Prognosis

Patients with acute idiopathic pericarditis have a good long-term prognosis. Cardiac tamponade rarely occurs in these patients and it is more common in case of a specific underlying etiology such as malignancy, tuberculosis, or purulent pericarditis. Constrictive pericarditis may occur in less than 1% of patients with acute idiopathic pericarditis and it is more common in

patients with a specific etiology. Gender may also predict clinical course; women generally have increased risk of complications, probably for their higher frequency of autoimmune etiologies.[25]

Patients with uncomplicated (*i.e.* low-risk) acute pericarditis can usually be discharged with a follow-up program to assess the efficacy of treatment. Instead, high-risk patients should be admitted to the hospital in order to start appropriate therapy and clinical observation. Patients with a high-risk pericarditis generally have fever (>38ºC), subacute course, evidence suggesting cardiac tamponade, a large pericardial effusion (*i.e.* an end-diastolic echo-free space of more than 20 mm), failure to show clinical improvement following seven days of appropriately dosed NSAID and colchicine therapy, therapy with vitamin K antagonists or novel oral anticoagulants, acute trauma, elevated cardiac troponin and a history of immunosuppression.

Treatment

Treatment of acute pericarditis should target the underlying etiology. The goals of treatment are relief of pain, resolution of inflammation (and, if present, pericardial effusion), and prevention of recurrence. Patients with pericarditis can be treated as outpatients, except for those at high risk that require hospital treatment. The treatment of patients with recurrences is not very different to treatment of a first episode of acute pericarditis. Aspirin or NSAIDs remain the mainstay of therapy. Colchicine is recommended on top of standard anti-inflammatory therapy in order to improve remission rates and prevent recurrences. In cases of incomplete response to NSAIDs and colchicine, corticosteroids may be used, but they should be added at low to moderate doses.[1]

Aspirin or non-steroidal anti-inflammatory drugs

The choice should be based on physician's experience as well as on history of efficacy and tolerability in the single patient. A NSAID that was effective in a previous attack should be the favorite choice. Ibuprofen and aspirin are the most used. Indomethacin is perhaps the most powerful. Comorbidities are also important: for example, aspirin is the preferred choice in patients with ischemic heart disease or when a patient is already on antiplatelet treatment or should be treated with for other reason. Naproxen is an alternative in these situations. On the other hand, indomethacin and other NSAIDs should be avoided in patients with coronary artery disease. In a hospitalized patient aspirin or NSAIDs should be administered intravenously (*i.e.* indomethacin 100 mg in 250 mL of saline in continuous infusion in a day). The highest tolerable dose of each medication should be used in severe cases assuring a continuous anti-inflammatory coverage throughout the day. In fact, a common mistake is to use too low doses. Aspirin should be used at the dose of 2 to 4 g/day; ibuprofen 1200-2400 mg/day; indomethacin 75-150 mg/day. Administration of NSAIDs should be well distributed in the day. For example, for aspirin, ibuprofen or indomethacin, each dose should be taken every 8 h in order to guarantee a full coverage of 24 h.

The duration of optimal treatment and the need to reduce the dose have not been tested in clinical trials. It is well established that the full dose regimen should be offered at least until normalization of CRP values and initial clinical remission. This may take months, especially in patients with history of recurrent pericarditis. The side effects of NSAIDs are well known. The most serious are ulcers, bleeding (that are more common in the first weeks), kidney failure. Aspirin use should be more cautious in patients with initial impaired renal function, erosive gastritis, peptic ulcer, gout, platelet and bleeding disorders. NSAIDs use should be more cautious in patients with cardiac dysfunction, hypertension, renal or hepatic impairment, patients receiving anticoagulants. However, in most patients these medications are taken for months without causing significant side effects. Proton pump inhibitors should be provided to all patients under aspirin or NSAIDs treatment.

Failure to respond to aspirin or NSAID therapy within weeks suggests that a cause other than idiopathic or viral pericarditis is present. In such instances, a search for the etiology should be performed and hospitalization may be suggested for symptom control and to expedite the diagnostic evaluation. The main causes to be ruled out include tuberculosis or other bacterial forms of pericarditis, cancer (especially lung cancer, breast cancer, and lymphomas and leukemias), post-cardiac injury syndromes, and systemic inflammatory diseases.[14,26,27,28]

Colchicine

Colchicine is always indicated, even in the first attack, but especially in case of recurrence and it should be added to the NSAIDs, not replacing them.[1] Colchicine therapy is able to improve the response to traditional anti-inflammatory therapy and to reduce the relapse rate by at least 50%.

Side effects are gastrointestinal including nausea, vomiting, diarrhea (7% for low doses, up to 10-15% for daily doses >1 mg), abdominal pain and elevation of transaminases. Other anecdotal side effects are bone marrow suppression (less than 1%) and reversible alopecia (0.6%). Colchicine interacts with macrolide antibiotics, in particular clarithromycin, so dose should be halved while these drugs are administered. Other im-

portant drug interactions include statins (both drugs are myotoxic), calcium channel blockers and cyclosporine.

To improve patient compliance and minimize the risk of side effects, colchicine should be administered in low, weight-adjusted doses (0.5 mg once daily for patients <70 kg, 1 mg once daily or 0.5 mg twice daily for patients >70 kg) without loading dose. Dose reduction is necessary for patients with renal impairment, debilitated patients and the elderly.

Therapy should last at least 6 months, but if recurrences are frequent and colchicine is well tolerated the duration can reach some years. At this point discontinuation is discussed with the patient, explaining that cases of recurrences after colchicine discontinuation have been reported. Even for colchicine, suspension should not be abrupt but gradual. Appropriate monitoring of the therapy is reached through chemistry (renal function, transaminases, creatine kinase and blood count) after 1 month and then in case of new symptoms or signs that may suggest and adverse event or a possible drug interaction.[29]

Glucocorticoids

Although corticosteroids provide rapid control of symptoms, they increase the risk of chronicity, recurrences, and side effects. They should not be used for initial treatment of acute pericarditis, but may be considered in patients with contraindications or failure to aspirin/NSAIDs, or when the cause of pericarditis is an autoimmune disease or uremia.

In most cases they should be considered only after the use of high dosages NSAIDs and added to aspirin/NSAIDs and colchicine as a triple therapy in cases of incomplete clinical control of the disease, particularly in adults, but at low to moderate doses (*i.e.*, prednisone 0.2-0.5 mg/kg/day in adults). If used, they should be prescribed at the lowest effective dose (*i.e.*, prednisone 0.2-0.5 mg/kg/day or equivalent) until resolution of symptoms and CRP normalization; tapering should be particularly slow.

The 2015 European Society of Cardiology (ESC) guidelines[1] propose the following tapering scheme: i) daily dose >50 mg - Taper 10 mg/day every 1 to 2 weeks; ii) daily dose 25 to 50 mg - Taper 5 to 10 mg/day every 1 to 2 weeks; iii) daily dose 15 to 25 mg - Taper 2.5 mg/day every 2 to 4 weeks; iv) daily dose <15 mg - Taper 1.25 to 2.5 mg/day every 2 to 6 weeks.

A number of non-randomized studies suggest that glucocorticoid therapy, especially in the early phase of disease, is associated with more adverse effects, a more prolonged disease course and higher recurrence risk.[30-32]

A critical threshold for recurrences is a 10 to 15 mg/d dose of prednisone or equivalent. At this threshold, very slow decrements (1.0 to 2.5 mg) in about 2-6 weeks are useful. In cases of recurrence every effort should be made not to increase the dose or to reinstate corticosteroids.

Every decrease in corticosteroids dose should be done only if the patient is asymptomatic and CRP is normal. Calcium intake (supplement plus oral intake) 1200-1500 mg/d and vitamin D supplementation 800-1000 IU/d should be offered to all adult patients receiving glucocorticoids. Moreover, bisphosphonates are recommended to prevent bone loss in all men >50 years and postmenopausal women in whom long-term treatment with glucocorticoids is initiated at a dose >5.0-7.5 mg/d of prednisone or equivalent. Acceleration in tapering corticosteroids plays a role in increasing risk of recurrences.[13]

Triple therapy and slow tapering: a magic bullet

A protocol including non-steroidal anti-inflammatory drugs at high dosage, colchicine, corticosteroids at low doses, reassurance and close clinical monitoring generally allows to obtain a good control of the disease also in the most severe cases.[1]

After obtaining a complete response, tapering should be done with a single class of drugs at a time. The order of discontinuation is: steroids, NSAIDs and at last colchicine. Steroid discontinuation may require from 2 to 10 months. During this time NSAIDs are used at low or high doses according to the clinical condition. After corticosteroids stable discontinuation, NSAIDs dosages should be gradually tapered, while colchicine must be the last drug to be stopped. Each tapering should be attempted only if symptoms are absent and CRP is normal. For these reasons the length of therapy may extend for months or even years in the most difficult cases. To control the pain, it is often useful to add other analgesics, like paracetamol or codeine or tramadol.

Immunotherapy and interleukin-1 inhibition

Immunotherapy is an alternative approach to treat refractory recurrent pericarditis.[1] Three drugs have been proposed: azathioprine, intravenous immunoglobulins (IVIg) and anakinra. Azathioprine and IVIg have been used in case reports or case series.[30] Despite their effectiveness IVIg have a high cost and lack good evidence.

Anakinra is a recombinant IL-1 receptor antagonist; it inhibits the action of IL-1, which is involved in the intracellular signaling pathway for prostaglandin release by macrophages and in chemotaxis of monocytes, lymphocytes and polymorphonuclear leukocytes, in the activation of T cells and in the stimulation of metalloproteinases. Anakinra was initially registered for the treatment of rheumatoid arthri-

tis but has found its niche in the treatment of several rare autoinflammatory diseases. A double-blind randomized controlled trial (AIRTRIP-The Anakinra-Treatment of Recurrent Idiopathic Pericarditis)[31] formally demonstrated the efficacy of anakinra in 21 patients with corticosteroid-dependent and colchicine-resistant recurrent pericarditis with elevated CRP. Anakinra obtained quick symptoms relief in a few days and allowed steroid discontinuation in all patients within 6 weeks. It is administered as a once daily subcutaneous injection at the dose of 100 mg in adults (1-2 mg/kg/d in children) for six months.[4] Recurrences can occur if tapering is too rapid. Tapering regimes are not established, and it is very difficult to propose a universal tapering regimen. A possible scheme might be to withdraw a dose every month after a full control of the disease has been reached. The drug is generally well tolerated. The most common adverse events are skin reactions at the site of injection, neutropenia and mild elevation of transaminases.

Interventional treatments

Medical therapy alone is effective in most patients with acute pericarditis. However, some circumstances may require pericardiocentesis and/or pericardial drainage: i) moderate to large pleural effusion, especially if hemodynamically significant, causing cardiac tamponade or symptomatic and refractory to medical therapy; ii) suspected neoplastic or bacterial etiology.

Prolonged catheter drainage of a pericardial effusion might be an effective means of preventing fluid re-accumulation. Catheter drainage may be required for several days, and the catheter should not be removed until drainage stops or is minimal. If significant drainage continues for more than three to four days, a pericardial window should be considered (communication between the pericardial space to the pleural cavity).

If there is evidence of constrictive pericarditis, the treatment is pericardiectomy. Pericardiectomy may be considered for frequent and highly symptomatic recurrences of pericarditis resistant to medical treatment. However, its efficacy is unproven and should be considered only in exceptional cases.[1]

Lifestyle limitations

Avoiding of physical activity beyond normal sedentary activities is recommended in all patients with myopericarditis. In case of isolated pericarditis, return to exercise is permissible when there is no further evidence of active disease in non-athlete.

For athletes, an expert consensus identified the need for a minimal 3-month-period of stopping of competitive activities until remission and normalization of findings. Presence or suspicion of myocardial involvement leads to contraindication of physical exercise for at least 6 months from the onset of the illness.[1]

Conclusions

In order to provide evidence-based recommendations for managing patients with pericarditis, we verified the existence of guidelines and reviews (including systematic reviews) on this subject.[33-36] We have therefore considered the following documents: i) *2015 ESC Guidelines for the diagnosis and management of pericardial diseases*;[1] ii) *Evaluation and Treatment of Pericarditis: A Systematic Review*;[29] iii) *Recurrent Pericarditis: Modern Approach in 2016*;[37] iv) *Acute Pericarditis: Diagnosis and Management*.[38]

These documents have been evaluated by four separate authors with the Appraisal of Guidelines, Research and Evaluation II (AGREE II) method, in order to find the best guidelines in quality.[36] The AGREE II method is a 23-item tool comprising six quality domains: i) scope and purpose; ii) stakeholder involvement; iii) rigor of development; iv) clarity of presentation; v) applicability; vi) editorial independence. Each author evaluated every item by assigning a score between one (*strongly disagree*) and seven (*strongly agree*). Domain scores are calculated by summing up all the scores of the individual items in a domain and by scaling the total as a percentage of the maximum possible score for that domain. It is recommended that each document is assessed by at least two appraisers and preferably four, as this will increase the reliability of the assessment.[36]

2015 ESC Guidelines prove to be the best ones, especially in terms of rigor of development, due to the link between the recommendations and the supporting evidence, and in clarity of presentation. Moreover, they prove to have editorial independence and the target users are all the relevant professional groups. Imazio's systematic review published on JAMA in 2015 reveals clarity of scope and the population to whom the document is meant to apply is specifically described; a high score was assigned to rigor of development, especially in the criteria for selecting the evidence and in the link between the recommendations and the supporting evidence, although it is not clear if the document has been externally reviewed by experts prior to its publication.[29] The review proves to have editorial independence, but it is not well supported with tools for application.

2016 Imazio's article about management of pericarditis clearly describes the objectives and the clinical questions covered. It proves to have clarity of presentation, but not a strong rigor of development, in fact it is not a systematic review.[37]

2014 American family physician recommendations used systematic methods to search for evidence, but it is not clear if they have been externally reviewed by experts, and a procedure for updating the recommendations is not provided, in fact they are not true guidelines. A high score was assigned to clarity of presentation and also in editorial independence.[38]

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