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REVIEW ARTICLE

Untying the Gordian knot of pericardial diseases: A pragmatic approach

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Abstract Pericardial disorders constitute a relatively common cause of heart disease. Although acute pericarditis, especially the idiopathic forms that are the most prevalent, is considered a benign disease overall, its short- and long-term complications, namely, recurrent pericarditis, cardiac tamponade and constrictive pericarditis, constitute a matter of concern in the medical community. In recent years, several clinical trials contributed to redefining our traditional approach to pericardial diseases. In this review, we provide the most recent evidence concerning diagnosis, treatment modalities and short- and long-term prognosis of the most common pericardial disorders.

Pericardial diseases encompass a wide spectrum of clinical conditions, ranging from benign and self-limiting forms to life-threatening conditions.[1,2] From a practical point of view, the main pericardial syndromes include acute and recurrent pericarditis either idiopathic or secondary with or without concomitant pericardial effusion, chronic constrictive pericarditis and isolated pericardial effusion without evidence of ongoing pericardial inflammation.[3]

In recent years, several clinical trials focused on pericardial diseases have enhanced our knowledge in this context and contributed to the development of effective and safe treatments, thus redefining several aspects of our

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traditional view of pericardial diseases. The present review aims to emphasize the most important advances in the field of pericardiology and to provide helpful 'tips and tricks' for an efficacious evidenced-based approach to the main pericardial syndromes.

1. Acute pericarditis

The lack of well-established criteria for the diagnosis of acute pericarditis was revealed to be an important confounding factor in the recent past, causing important methodological divergences between investigations. Unfortunately, the absence of a pathognomonic marker, such as troponins for myocardial necrosis, accounts for this inconvenience. More recently, however, an expert consensus on the diagnosis of acute pericarditis has contributed to overcoming this inconvenience.[4] Indeed, acute pericarditis is considered when 2 out of the following criteria are fulfilled: i) retrosternal chest pain sharing several features with ischemic pain, which, however, worsens in, for example, a supine position, deep inspiration, cough, and swallowing and is relieved in the upright position and by leaning forward; ii) pericardial friction rub, which is pathognomonic for pericarditis but is unfortunately present in one-third of patients;[5] iii) typical electrocardiographic features with evolution in four stages in 60% of cases (namely, diffuse concave ST segment elevation with concomitant PR depression in the first stage, return to baseline of the latter deviations and T wave flattening in the second stage, diffuse T-wave inversion in the third stage, and electrocardiographic normalization in the fourth stage);[2] and iv) new-appearing or worsening pericardial effusion, which is observed in 60% of cases (80% mild, and 10% either moderate or large).[6] In the abovementioned main diagnostic criteria, 2 more variables have been added, this time as supportive findings. The first is CRP elevation, although apart from being found normal in ~22% of cases at presentation,[7] has the additional limitation of low overall specificity. The second is thickening and late gadolinium enhancement at the pericardial level in the cardiac MRI (cMR), which is indicative of pericardial inflammation.[5,8,9] It is stressed that both MRI and computed tomography are considered as a second line option in the diagnostic work-up process of pericardial diseases and should be performed when the rest of the findings are inconclusive.[2]

The causes of acute pericarditis include infectious and non-infectious forms and are summarized in Table 1.[4] With respect to the diagnostic approach, local epidemiology should be always taken into account. For example, tuberculous pericarditis, which is a rare condition in the Western word, is the most common cause of acute pericarditis (~70–80%) in sub-Saharan Africa.[4] Identification of the causative infective agent in viral forms is not necessary in every day practice since it does not add any therapeutic or prognostic information.[10] Although troponins do not seem to have a prognostic impact on acute pericarditis, they should be evaluated to exclude myopericarditis.[4]

Hospitalization in acute pericarditis should be restricted only to high risk patients (high risk of non-viral, non-idiopathic etiology and complications during follow-up), who should be investigated and treated accordingly. The major criteria validated by multivariate analysis include large pericardial effusion (>2 cm in diastole) with or without tamponade, a fever >38°C, subtle presentation over the course of several days, and lack of responsiveness to the non-steroidal anti-inflammatory treatment within 1 week of therapy.[4] Minor clinical poor prognostic criteria include myopericarditis, immunodepression, traumatic pericarditis and oral anticoagulant therapy. Patients with one or more of the abovementioned criteria should be hospitalized and subjected to an extensive etiologic search.[4]

Restriction of physical activity should be recommended in all patients with acute pericarditis; however, this recommendation applies only until complete clinical remission along with CRP normalization. Competitive sports are allowed at least 3 months after the index episode.[11]

Regarding medical treatment, the combination of aspirin-NSAIDs with colchicine 0.5 mg twice daily (or 0.5 mg once daily if <70kg) for 3 months is the mainstay approach.[2,11,12] Aspirin and ibuprofen are the medications most frequently administered worldwide. Although they are highly effective in controlling symptoms, neither of them seem to affect the natural history and complication rates of acute pericarditis.[1] Particular attention should be paid in using the highest tolerable doses of each medication and assuring continuous anti-inflammatory coverage throughout the day (e.g., each dose given every 8 hours for ibuprofen and aspirin).[11] The optimal treatment length and the need for dose tapering have not been tested in clinical trials, and similarly, no head to head comparisons between anti-inflammatory agents have been performed. It is well-established, however, that the full-dose regimen should be offered at least until normalization of CRP values. Thus, CRP monitoring is extremely helpful in individualizing the duration of treatment. Although of doubtful benefit, several experts recommend dose tapering of NSAIDs after initial clinical remission and CRP normalization.[2,11] Dose

Table 1 Most common causes of acute pericarditis.

Infectious (2/3 of cases)	Non-infectious (1/3 of cases)
Viral (most viral forms are labeled idiopathic since it is often difficult and technically demanding to reveal an underlying viral infection)	Autoimmune (including systemic autoimmune, autoinflammatory diseases and pericardial injury syndromes)
Bacterial (tuberculous in 4%–5% of cases)	Neoplastic
Fungal or parasitic (extremely rare)	Metabolic
	Traumatic
	Drug related (rare)

tapering should, however, respect drug pharmacokinetics and offer antiinflammatory protection throughout the day.[11] Details about the treatment schedule in acute pericarditis are depicted in Table 2.[11]

Colchicine should be administered in every case of acute pericarditis (unless contraindicated) as it is the only medication that has dramatically reduced (halved) the rate of recurrences. To overcome potential problems with patients' compliance and/or drug withdrawal, dose adjustment should be performed according to age, body weight and renal function (Table 2).[13]

Corticosteroids are a second-line treatment option in patients with acute pericarditis. It seems that a dose between 0.2 and 0.5 mg/kg/die of prednisone (or an equivalent dose of an alternative agent) outmatches the dose of 1—1.5 mg/kg/die that is recommended in guidelines regarding both safety and efficacy.[2,4] The main problem associated with steroid administration in pericarditis concerns the higher rate of recurrences, probably caused by the enhanced viral replication due to immunosuppression. Despite this indisputable fact, steroid use should not be 'demonized' as it is a valuable treatment option in several conditions. To rephrasing a saying of Abraham Lincoln, 'the problem with steroids relates not to the use of a bad thing but to the abuse of a good thing.' In fact, steroids should be used when aspirin/NSAIDs are ineffective after at least 1 week of treatment, provided that the highest tolerable dose has been prescribed, in cases of true allergy of intolerance to the latter medications, in secondary (specific) cases where steroids constitute the recommended treatment (e.g., systemic inflammatory diseases), in advanced kidney disease, in pregnant women beyond the 20th week of gestation, and probably in cases with intense inflammation and/or concomitant pleuro-pericardial involvement (e.g., post-pericardiotomy syndrome).[1,4,5,11] A gradual tapering of corticosteroids is essential, with each reduction made only in absence of symptoms and after CRP normalization, particularly for dosages of prednisone lower than 10—15 mg daily.[4]

Last but not least, gastroprotection should be provided to all patients under aspirin-NSAIDs treatment, and vitamin D, calcium and diphosphonates should be administered when >5—7.5 mg of prednisone are prescribed to premenopausal women and men aged >50 years for ≥3 months.[4,5,11,14]

Table 2 Empiric treatment schedule in acute and recurrent pericarditis.

Drug	Recommended attack dose	Treatment length with attack dose	Tapering
Aspirin	750—1000 mg tid (range 1.5—4 g/daily)	Until symptoms and CRP normalization	Each week when CRP is normalized (i.e., 1000 mg tid for 1 week, 750 mg tid for 1 week then 500 mg tid for 1 week)
Ibuprofen	600 mg tid (range 1.2—3.2 g/daily)	Until symptoms and CRP normalization	Each week when CRP is normalized (i.e., 600—400—600 mg/day for 1 week, 400—400—600 mg/day for 1 week, then 400 mg tid for 1 week)
Indomethacin	25—50 mg tid	Until symptoms and CRP normalization	Each week when CRP is normalized (i.e. 50—25—50 mg/day for 1 week, 25—25—50 mg/day for 1 week, then 25 mg tid for 1 week)
Colchicine	Attack dose not necessary. 0.5 mg bid (0.5 mg/day if <70 kg or intolerance, age >70 years. Dose adjustment in reduced creatinine clearance)	First attack: 3 months, recurrence: at least 6 months	May be required in recurrent forms according to some authorities
Prednisone	0.2—0.5 mg/kg/day (or equivalent dose of another corticosteroid)	Until symptoms and CRP normalization	Tapering when CRP is normalized. Slow tapering at the threshold for the individual patient for recurrences
Anakinra	1—2 mg/kg, up to 100 mg sc daily	To be established. Long-term administration (6—12 months) is usually required.	Recommended by most authorities
Azathiorpine	1.5—2.5 mg/kg/day	Depends on the individual patient. Usually, >1 year	Not recommended
Intravenous immunoglobulins	400—500 mg/kg/day	5 consecutive days	Repeated cycles may be required according to the clinical response

CRP = C-reactive protein, bid = twice a day, tid = three times a day, sc = subcutaneously.

Prognosis of acute pericarditis is excellent in the idiopathic forms, with serious complications being uncommon (tamponade 1.2% and permanent constriction ~0.5% in a 60-month follow-up period).[15] The rate of recurrence is 15–30% depending on the colchicine use, and the great majority of recurrences are expected within 18–20 weeks.[1,12,16] Myocardial involvement (myopericarditis) does not seem to affect long-term prognosis, whereas cases of perimyocarditis (prevalent myocardial involvement, with affected contractility and regional wall motion abnormalities) should probably be regarded and treated in the same way with pure myocarditis treatment.[4] The most severe complication of acute pericarditis is cardiac tamponade. Timely recognition and treatment of tamponade is of paramount importance since hemodynamic collapse can lead rapidly to death. Recently, the European Society of cardiology proposed a scoring system that aims to affect the decision regarding the timing of pericardial drainage.[17] The abovementioned score-system takes into account several parameters including etiology, clinical presentation, and imaging and offers information about the indication of immediate or urgent need for drainage (either percutaneous or surgical), or about the possibility of scheduling the procedure safely on an elective basis and transferring patients to a specialized institution.

2. Recurrent pericarditis

Recurrent pericarditis is the most problematic complication of acute pericarditis due to its detrimental impact on patients' quality of life. In the era of colchicine, the rate of recurrence has been dramatically reduced to approximately 17%, at least in idiopathic forms.[12,16] Patients with a first recurrence have an even higher percentage of a second one (up to 50%) and approximately half of all cases exhibit 1–2 recurrences (although individual cases with many recurrences have been reported).[1,2,16,18]

The mechanisms involved in pericarditis recurrences classically include infections (exacerbations of the initial one or reinfections), an inadequate initial full dose regimen or too rapid drug tapering, or autoimmunity, which is believed to account for 2/3 of cases.[16,19–21] A novel piece of research, however, has recently added another possible mechanism involved in relapse appearance, namely, autoinflammation.[19,21] Autoinflammatory diseases include those genetic disorders characterized by primary dysfunction of the innate immune system. These diseases appear with recurrent episodes of serosal inflammation, leukocytosis, and familial occurrence. Examples are Familial Mediterranean Fever and the tumor-necrosis factor receptor-1-associated periodic syndrome (TRAPS), which in a relevant investigation accounted for 6% of recurrent idiopathic pericarditis cases.[22] Autoinflammatory disorders should be considered in cases of early onset of the disease, positive family history for pericarditis, late relapses (>18–20 months), and most importantly, failure of colchicine therapy and need for immunosuppression to control the disease.[22]

It is reasonable for diagnostic work-up in recurrent cases to be more extensive and include second option tests and diagnostic pathways, in an effort to unveil secondary and potentially treatable secondary conditions. It is emphasized that idiopathic recurrent pericarditis is not necessarily a life-time diagnosis and patients should be periodically reassessed for clinical and laboratory markers of secondary forms. In a relevant investigation with long-term follow up, a secondary form emerged in ~10% of cases, mainly a connective tissue disease.[23]

As already described, for acute pericarditis, the treatment options for recurrent forms include aspirin-NSAIDs, colchicine and corticosteroids, and the overall management should be tailored in an individualized fashion.[1,3,4,24] Although the dose regimens are largely the same in acute and recurrent pericarditis, the treatment length should be more extended (perhaps doubled) in the latter, at least according to some experts.[4,25] CRP serum levels should be monitored in order to access treatment efficacy and schedule dose tapering and treatment length.[4] (Table 2).

Colchicine is the mainstay treatment in recurrent pericarditis. Its safety and effectiveness in this setting has been tested in several clinical trials including CORE, CORP and CORP-2.[26–28] Colchicine was proved effective (and safe) in the whole spectrum of recurrent pericarditis, such as first recurrence (CORE-CORP)[26,27] and multiple recurrences (CORP-2).[28] Thus, colchicine use has a class I indication in recurrent pericarditis, where the administration of 0.5 mg bid (or adjusted regimen where required) halves the percentage of first or subsequent recurrences.[2] Steroids administered at the lower effective dosages constitute a valid treatment option in all clinical scenarios already described for acute pericarditis. Dose tapering should be very slow at the critical threshold for the individual patient for recurrences.[2] In case of symptom recurrence during steroid tapering, administration of aspirin or NSAIDs is recommended in an effort to avoid an increase of in the steroid dose, which leads to vicious cycles.[4]

In recent years, the term refractory idiopathic recurrent pericarditis (or colchicine-resistant steroid-dependent pericarditis) has been introduced in clinical practice to describe hard-to-control cases with multiple recurrences that require high doses of corticosteroids (namely, prednisone >15 mg daily or equivalent) for long periods to be controlled.[4] True refractory pericarditis accounts for approximately 5% of recurrent cases.[5] Referral of these difficult-to-treat patients to specialized centers for evaluation and treatment is strongly encouraged. According to the best available evidence, treatment options in true refractory recurrent pericarditis include the following options. The first consists of combined triple therapy including corticosteroids, colchicine and aspirin or NSAIDs. Aspirin-NSAIDs should preferably be added when recurrence appears, or earlier when the dose threshold of steroids for relapses is being reached.[4] In patients receiving steroids/NSAIDs to control symptoms, the decision to withdraw steroids or NSAIDs first should be considered on an individual basis, taking into account the patient's tolerance and overall profile. Nevertheless, any drug dose tapering or discontinuation should be preceded by CRP normalization.

Alternatives to the abovementioned treatments include classic immunosuppressant (mainly azathioprine), anakinra, and intravenous immunoglobulins. Because all the above options are off-label and adverse effects are a serious matter of concern, all potential candidates should

be informed of possible side effects in detail and an informed consent is mandatory. Azathioprine is the most widely used agent over time in this context. Data on its efficacy are available from a retrospective study including 40 cases.[29] The dose administered was 1.5—2.5 mg/kg/day (mean 2.12 mg) and the mean time period on treatment was ~14 months (Table 2). The medication turned out both safe and effective in reducing the number of recurrences. Most importantly, in a considerable proportion of patients (~60%), it caused sustained remission of the disease after discontinuation of steroids. It should be stressed that azathioprine has a delayed onset of action (>1.5 months) and thus it is not suitable for the treatment of the acute attack.

Anakinra is another treatment option recently introduced in the medical armamentarium for recurrent pericarditis. It is an interleukin-1 antagonist administered at a daily dose of 100 mg in adults that is delivered through a subcutaneous injection for at least 6—12 months.[30—33] In a recent systematic review of all published cases, anakinra turned out to be a safe and highly effective steroid sparing agent.[32] The drug allowed immediate clinical remission with CRP normalization within a few days. During the full-dose regimen, no cases of symptom recurrence have been reported. After drug discontinuation, however, recurrences appear early (within few weeks), at a rate of ~75%. Gradual tapering according to preliminary observations seems to lower the rate of recurrences.[32]

Finally, according to a recent systematic review, intravenous immunoglobulins administered at a daily dose of 400 to 500 mg/kg for 5 consecutive days constitute a well-tolerated, rapidly acting, and effective steroid-sparing option in refractory recurrent pericarditis.[34]

We wish to stress that the abovementioned off-label alternatives to conventional treatment are not based on solid evidence and treatment choices should depend on local expertise and availability. Pericardiectomy today is rarely required and should be regarded as the last resort in refractory pericarditis cases presenting with recurrent tamponade, and in patients unable to tolerate the aforementioned conventional treatment. In centers of excellence, the perioperative mortality and major morbidity and are very low (0 and 3%, respectively).[35]

The prognosis of recurrent pericarditis is excellent in idiopathic forms, while in secondary ones, the underlying condition mainly affects the long-term outcome.[4,36] In a systematic review of all publications including 230 patients with a follow-up of ~60 months, the rate of tamponade was 3.5% (occurring mostly during the initial attack), whereas cases of constrictive pericarditis and left ventricular dysfunction were never reported.[37]

Beyond efficacious treatment, the primary goal for health physicians managing pericardial diseases should be the prevention of recurrences, rather than their treatment. In this context, the inappropriate use of medical therapies may account for disease recurrence at least in a subset of cases. For instance, the early (and unjustified) use of steroids may facilitate viral replication and disease recurrence. Moreover, rapid tapering or discontinuation of anti-inflammatory therapy before complete symptom remission and CRP normalization, as well as colchicine non-use, are associated with recurrent disease.[4] Additional research is urgently required to identify those patients prone to recurrences and clarify the mechanisms leading to disease recurrence.[38]

3. Constrictive pericarditis

Constrictive pericarditis along with pericardial tamponade and recurrent pericarditis constitute the most common complications of pericarditis.[15] The appearance of pericardial constriction is rather rare in acute idiopathic pericarditis and exceptional as already mentioned in recurrent pericarditis. In tuberculosis endemic areas, however, constrictive pericarditis is a major health care problem with high morbidity and mortality.[4,15] Thus, awareness of the local epidemiology is very important in tracking, investigating and diagnosing the disease.

Concerning the diagnostic work-up in constrictive pericarditis, today, echocardiography with the application of novel echocardiographic techniques (including tissue Doppler imaging and speckle tracking), computed tomography, and cardiac MRI (cMR) with gadolinium have improved diagnostic accuracy and allowed the diagnosis of the disease at earlier stages before myocardial involvement, which negatively affects patient outcomes.[8] In particular, cMR with cine imaging highlights in an excellent way the interventricular interdependence observed in constriction pericarditis through the pathological motion (bounce) of the interventricular septum. Most importantly, with the use of modern imaging modalities, the use of cardiac catheterization, which is classically considered the gold-standard for the diagnosis of pericardial constriction, may be omitted on occasion. In the Mayo Clinic group's recently published echocardiographic criteria for the diagnosis of constrictive pericarditis, cardiac catheterization was not considered a prerequisite for the final diagnosis and it has been performed only in 48% of patients before operation.[39] It should be emphasized that increased pericardial thickness that has been traditionally considered an essential finding to diagnose constrictive pericarditis is not observed in 18% of surgically proven cases.[40]

Constrictive pericarditis has traditionally been considered a condition requiring surgical management, and total pericardiectomy is the recommended treatment option.[4,41] Patient candidates for surgical treatment are those needing chronic diuretic therapy and exhibiting increasing jugular venous pressure, evidence of hepatic impairment, and reduced exercise tolerance.[2,42] In contrast, surgical treatment is not indicated in early asymptomatic constriction or in advanced stages with myocardial fibrosis and severe functional impairment (NYHA class IV). The operative mortality in the latter cases is quite prohibitive (30—40% compared with 6—19% in a lower NYHA class).[2,42]

In recent years, the term transient constriction has been introduced in clinical practice by Sagrista-Sauleda et al. to describe a transitory constriction physiology observed in 9% of patients with acute effusive pericarditis during the resolution phase of the effusion.[43] In the authors' experience, constriction in such cases regressed within a mean time of 2.7 months.

In a subsequent review published by the Mayo Clinic group, the rate of transient constriction in 212 patients first

presenting with echocardiographic findings of constrictive pericarditis was 17%.[44] The average time elapsed between initial diagnosis and resolution of the disorder in this database was 8.3 weeks. Interestingly, no transitory forms were observed in patients with constrictive pericarditis following radiation therapy. Patients with reversible constriction were treated with various medication regimens (mainly NSAIDS and steroids), whereas spontaneous haemodynamics normalization was observed in 14% of cases.

To summarize, the important new concept that arose from the above observations is that in hemodynamically stable patients who present for the first time with features suggesting constrictive pericarditis, a trial of anti-inflammatory treatment (probably of 2−3 months duration) may be offered before referral for total pericardiectomy.[4]

The role of imaging in predicting transient vs. permanent forms of constriction is very important. Baseline late gadolinium enhancement (LGE) pericardial thickness >3 mm (sensitivity 86% and specificity 80%) and qualitative LGE intensity (moderate or severe in 93% of transient forms and 33% in permanent, $p = 0.002$) emerged as the most powerful parameters for the prediction of transient forms.[45] In addition, higher baseline CRP values were able to differentiate transient and permanent forms (59 ± 52 versus 12 ± 14 mg/L, $p = 0.04$).[45]

4. Chronic idiopathic pericardial effusion

This section addresses the incidental finding of pericardial effusion in either symptomatic or asymptomatic patients in the absence of clinical and laboratory findings (mainly CRP elevation) suggesting acute pericarditis.

It is implied than even in the absence of evidence of a specific cause, a detailed medical history and clinical examination as well as a group of blood tests possibly including screening for common causes of pericardial effusion (such as thyroid and kidney function tests and screening for connective tissue diseases) should be undertaken in an effort to establish a secondary condition, especially for moderate and large effusions.[4]

Pericardial effusion is defined as chronic if it persists for longer than a 3-month time period.[2,4] In the presence of chronic pericardial effusion, it is reasonable for the treating physician to express concerns with respect to the evolution of the disorder towards cardiac tamponade and hemodynamic collapse. In this context, the amount of pericardial effusion may have a predictive role. Indeed, small pericardial effusions have been traditionally regarded as a benign condition, and as such, not requiring specific treatment and close follow-up.[4] Concerns about the latter approach were raised by a recent publication where even small sized pericardial effusions (<1 cm in diastole) were found to be independently associated with mortality, even after adjustment for several possible confounders.[46] Although the abovementioned (and unexpected results) need confirmation in future trials, the latter study made a substantial contribution in the assessment of the progression (or regression) of small-sized pericardial effusions. During a mean follow up of 2.3 ± 1.9 years, 60% of effusions were resolved, 28% remained unchanged and 5% increased, although no case of tamponade was recorded.[46]

In cases of moderate pericardial effusion (sized>1 cm and <2 cm in diastole) the index of suspicion of an underlying condition should be high since approximately 60% of cases with moderate to large effusions are associated with secondary conditions.[4] Pericardiocentesis, if technically feasible, should be deserved to symptomatic patients or when a neoplastic or bacterial etiology (including tuberculosis) are suspected.[47]

In the presence of a large pericardial effusion with hemodynamic impairment, pericardicentesis is a mandatory

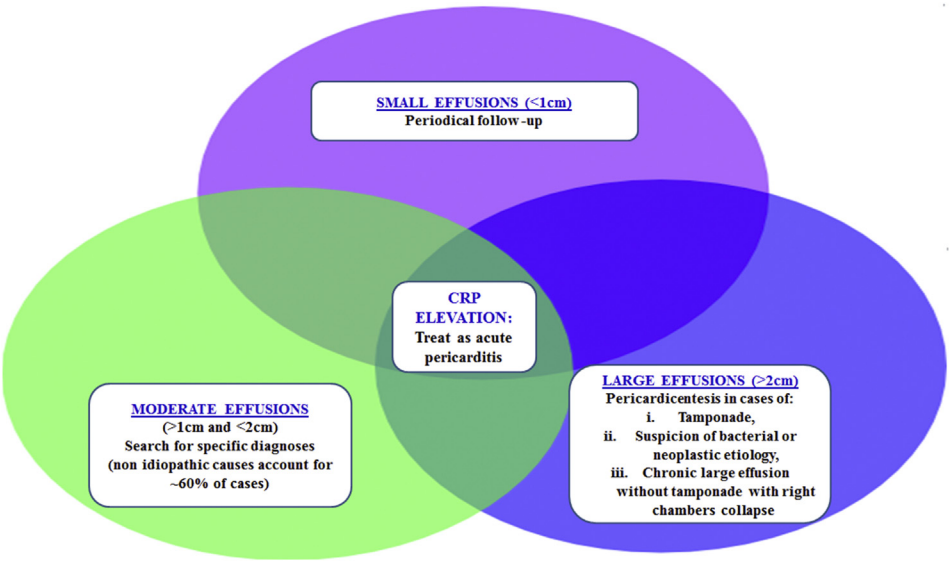

Figure 1 Recommended triage of patients with pericardial effusion. The intersecting part of the 3 cycles corresponds to cases with CRP elevation, which should be treated according to the recommendations provided for acute pericarditis. The free parts of the cycles include pericardial effusion cases without CRP elevation. In the latter cases, the management depends on the degree (small, moderate and large) of pericardial effusion.

procedure to prevent circulatory collapse.[4] Notably, when cardiac tamponade occurs in the absence of inflammatory markers, the possibility of neoplastic disease is quite high.[4] In the absence of cardiac tamponade, the indications of pericardiocentesis are the same as those above reported for moderate effusions. According to some authorities, any large chronic idiopathic pericardial effusion, particularly in the presence of right chamber collapse, should be treated with pericardiocentesis as approximately 1/3 of cases may progress to cardiac tamponade in the long term, either unexpectedly or in such contexts as acute pericarditis and chest trauma.[4,48]

Finally, in the absence of ongoing inflammation (i.e., elevated CRP) conservative treatment of chronic idiopathic effusions of any size with medical therapy (including aspirin-NSAIDs, colchicine and/or steroids) is not effective.[4] In Figure 1, the recommended approach for patients with chronic pericardial effusion is provided with respect to the presence or absence of inflammation and to the effusion site.

5. Conclusions

In recent years, several trials have changed our traditional clinical practice in the field of pericardial diseases concerning diagnostic work-up and medical therapy. It is important for physicians to become familiar with the current trends to treat their patients successfully according to the best available evidence. Although several pieces of the puzzle of pericardial disorders are still missing, ongoing clinical and basic research are expected to provide the rest of information needed to untie the Gordian knot of pericardial diseases.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Lazaros G, Vlachopoulos C, Stefanadis C. Idiopathic recurrent pericarditis: searching for Ariadne's thread. *Hellenic J Cardiol*. 2009;50(3):45—351.
2. Maisch B, Seferovic PM, Ristic AD, et al. Task Force on the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology. Guidelines on the diagnosis and management of pericardial diseases executive summary. *Eur Heart J*. 2004;25:587—610.
3. Imazio M, Adler Y. Pharmacological therapy of pericardial diseases. *Curr Pharm Des*. 2015;21:525—530.
4. Imazio M, Spodick DH, Brucato A, Trinchero R, Adler Y. Controversial issues in the management of pericardial diseases. *Circulation*. 2010;121:916—928.
5. Imazio M, Gaita F. Diagnosis and treatment of pericarditis. *Heart*. 2015;101:1159—1168.
6. Imazio M, Demichelis B, Parrini I, et al. Day-hospital treatment of acute pericarditis: a management program for outpatient therapy. *J Am Coll Cardiol*. 2004;43:1042—1046.
7. Imazio M, Brucato A, Maestroni S, et al. Prevalence of C-reactive protein elevation and time course of normalization in acute pericarditis: implications for the diagnosis, therapy, and prognosis of pericarditis. *Circulation*. 2011;123:1092—1097.
8. Cosyns B, Plein S, Nihoyanopoulos P, et al. European Association of Cardiovascular Imaging (EACVI) position paper: multimodality imaging in pericardial disease. *Eur Heart J Cardiovasc Imaging*. 2015;16:12—31.
9. Doulaptsis C, Cazacu A, Dymarkowski S, Goetschalckx K, Bogaert J. Epistenocardiac pericarditis. *Hellenic J Cardiol*. 2013;54:466—468.
10. Lazaros G, Vlachopoulos C, Stefanadis C. Extensive infectious panel testing for acute pericarditis: a ghost hunt? *Cardiology*. 2011;119:131—133.
11. Imazio M. Contemporary management of pericardial diseases. *Curr Opin Cardiol*. 2012;27:308—317.
12. Imazio M, Brucato A, Cemin R, et al. A randomized trial of colchicine for acute pericarditis. *N Engl J Med*. 2013;369:1522—1528.
13. Imazio M, Brucato A, Trinchero R, Spodick D, Adler Y. Colchicine for pericarditis: hype or hope? *Eur Heart J*. 2009;30:532—539.
14. Grossman JM, Gordon R, Ranganath VK, et al. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Care Res (Hoboken)*. 2010;62:1515—1526.
15. Imazio M, Brucato A, Maestroni S, et al. Risk of constrictive pericarditis after acute pericarditis. *Circulation*. 2011;124:1270—1275.
16. Imazio M. Idiopathic recurrent pericarditis as an immune-mediated disease: current insights into pathogenesis and emerging treatment options. *Expert Rev Clin Immunol*. 2014;10:1487—1492.
17. Ristić AD, Imazio M, Adler Y, et al. Triage strategy for urgent management of cardiac tamponade: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. 2014;35:2279—2284.
18. Imazio M. Treatment of recurrent pericarditis. *Expert Rev Cardiovasc Ther*. 2012;10:1165—1172.
19. Cantarini L, Imazio M, Brucato A, Lucherini OM, Galeazzi M. Innate versus acquired immune response in the pathogenesis of recurrent idiopathic pericarditis. *Autoimmun Rev*. 2010;9:436—440.
20. Lazaros G, Karavidas A, Spyropoulou M, et al. The role of the immunogenetic backgound in the development and recurrence of acute idiopathic pericarditis. *Cardiology*. 2011;118:55—62.
21. Cantarini L, Imazio M, Brizi MG, et al. Role of autoimmunity and autoinflammation in the pathogenesis of idiopathic recurrent pericarditis. *Clin Rev Allergy Immunol*. 2013;44:6—13.
22. Cantarini L, Lucherini OM, Brucato A, et al. Clues to detect tumor necrosis factor receptor-associated periodic syndrome (TRAPS) among patients with idiopathic recurrent acute pericarditis: results of a multicentre study. *Clin Res Cardiol*. 2012;101:525—531.
23. Brucato A, Brambilla G, Moreo A, et al. Long-term outcomes in difficult-to-treat patients with recurrent pericarditis. *Am J Cardiol*. 2006;98:267—271.
24. LeWinter MM. Acute pericarditis. *N Engl J Med*. 2014;371:2410—2416.
25. Lilly LS. Treatment of acute and recurrent idiopathic pericarditis. *Circulation*. 2013;127:1723—1726.
26. Imazio M, Bobbio M, Cecchi E, et al. Colchicine as first choice therapy for recurrent pericarditis: results of the CORE (COlchicine for REcurrent pericarditis) trial. *Arch Intern Med*. 2005;165:1987—1991.
27. Imazio M, Brucato A, Cemin R, et al. Colchicine for recurrent pericarditis (CORP): a randomized trial. *Ann Intern Med*. 2011;155:409—414.
28. Imazio M, Belli R, Brucato A, et al. Efficacy and safety of colchicine for treatment of multiple recurrences of pericarditis (CORP-2): a multicentre, double-blind, placebo-controlled, randomised trial. *Lancet*. 2014;383:2232—2237.
29. Vianello F, Cinetto F, Cavraro M, et al. Azathioprine in isolated recurrent pericarditis: a single centre experience. *Int J Cardiol*. 2011;147:477—478.

30. Lazaros G, Vasileiou P, Koutsianas C, et al. Anakinra for the management of resistant idiopathic recurrent pericarditis. Initial experience in 10 adult cases. *Ann Rheum Dis*. 2014;73:2215—2217.
31. Vassilopoulos D, Lazaros G, Tsioufis C, Vasileiou P, Stefanadis C, Pectasides D. Successful treatment of adult patients with idiopathic recurrent pericarditis with an interleukin-1 receptor antagonist (anakinra). *Int J Cardiol*. 2012;160:66—68.
32. Lazaros G, Imazio M, Brucato A, et al. Anakinra: an emerging option for refractory idiopathic recurrent pericarditis. A systematic review of published evidence. *J Cardiovasc Med (Hagerstown)*. 2016;17:256—262.
33. Lazaros G, Tousoulis D. Rheumatoid Arthritis and Atherosclerosis: Could Common Pathogenesis Translate Into Common Therapies? *Hellenic J Cardiol*. 2015;56:414—417.
34. Imazio M, Lazaros G, Picardi E, et al. Intravenous human immunoglobulins for refractory recurrent pericarditis. a systematic review of all published cases. *J Cardiovasc Med (Hagerstown)*. 2016;17:263—269.
35. Khandaker MH, Schaff HV, Greason KL, et al. Pericardiectomy vs medical management in patients with relapsing pericarditis. *Mayo Clin Proc*. 2012;87:1062—1070.
36. Lazaros G, Stefanadis C. Malignant pericardial effusion: still a long way to Ithaca. *Cardiology*. 2013;125:15—17.
37. Imazio M, Brucato A, Adler Y, et al. Prognosis of idiopathic recurrent pericarditis as determined from previously published reports. *Am J Cardiol*. 2007;100:1026—1028.
38. Vasileiou P, Tsioufis C, Lazaros G, et al. Interleukin-8 as a predictor of acute idiopathic pericarditis recurrences. A pilot study. *Int J Cardiol*. 2014;172:e463—e464.
39. Welch TD, Ling LH, Espinosa RE, et al. Echocardiographic diagnosis of constrictive pericarditis: Mayo Clinic criteria. *Circ Cardiovasc Imaging*. 2014;7:526—534.
40. Talreja DR, Edwards WD, Danielson GK, et al. Constrictive pericarditis in 26 patients with histologically normal pericardial thickness. *Circulation*. 2003;108:1852—1857.
41. Barbetakis N, Xenikakis T, Paliouras D, et al. Pericardiectomy for radiation-induced constrictive pericarditis. *Hellenic J Cardiol*. 2010;51:214—218.
42. Hoit BD. Management of effusive and constrictive pericardial heart disease. *Circulation*. 2002;105:2939—2942.
43. Sagristà-Sauleda J, Permanyer-Miralda G, Candell-Riera J, Angel J, Soler-Soler J. Transient cardiac constriction: an unrecognized pattern of evolution in effusive acute idiopathic pericarditis. *Am J Cardiol*. 1987;59:961—966.
44. Haley JH, Tajik AJ, Danielson GK, Schaff HV, Mulvagh SL, Oh JK. Transient constrictive pericarditis: causes and natural history. *J Am Coll Cardiol*. 2004;43:271—275.
45. Feng D, Glockner J, Kim K, et al. Cardiac magnetic resonance imaging pericardial late gadolinium enhancement and elevated inflammatory markers can predict the reversibility of constrictive pericarditis after antiinflammatory medical therapy: a pilot study. *Circulation*. 2011;124:1830—1837.
46. Mitiku TY, Heidenreich PA. A small pericardial effusion is a marker of increased mortality. *Am Heart J*. 2011;161:152—157.
47. Lazaros G, Imazio M, Tousoulis D. Percutaneous pericardiocentesis: safety first!. *Cardiology*. 2015;130:34—36.
48. Sagristà-Sauleda J, Angel J, Permanyer-Miralda G, Soler-Soler J. Long-term follow-up of idiopathic chronic pericardial effusion. *N Engl J Med*. 1999;341:2054—2059.