What's new in recurrent pericarditis?

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*No conflicts of interests to declare
Acute pericarditis is diagnosed in approximately 0.1% of hospitalized patients and accounts for 5% of emergency department visits for chest pain in the absence of myocardial infarction.

The incidence of acute pericarditis is ~27.7 cases per 100,000 population/year and in 2/3 of cases affect males.

Causes of acute pericarditis:

- Idiopathic (presumably viral) forms
- Forms secondary to one of the following conditions:
  - Uremia
  - Tuberculosis
  - Neoplasm
  - Autoimmune or inflammatory disease
  - Myocardial infarction
  - Postcardiotomy syndrome
  - Trauma
  - Aortic dissection
  - Endocrine disorders
  - Chest wall irradiation
  - Adverse drug reaction-toxins

Potential complications:
- Recurrent pericarditis
- Cardiac tamponade
- Constrictive pericarditis

References:
Complications of acute pericarditis

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Diagnosis of recurrent pericarditis

The patient should fulfill the following criteria

- A) a documented first attack of acute pericarditis
- B) recurrent chest pain compatible with pericarditis
- C) and one or more of the following signs:
  - Fever
  - Pericardial friction rub
  - Typical ECG changes (widespread ST-segment elevation and/or PR depression)
  - New or worsening or pericardial effusion
  - Elevation of white blood cells or markers of inflammation

Most common causes of recurrent pericarditis

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<th>Cause</th>
<th>Frequency</th>
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<tr>
<td>Idiopathic</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>Systemic Inflammatory Diseases and Pericardial Injury Syndromes*</td>
<td>5-10%</td>
</tr>
<tr>
<td>Autoinflammatory diseases</td>
<td>5-10%</td>
</tr>
<tr>
<td>Neoplastic pericardial diseases</td>
<td>5%</td>
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*post pericardiotomy syndrome, post myocardial infarction syndrome, post traumatic pericarditis

Diagnostic work up

Acute Pericarditis
Obligatory (class Ia)
- Auscultation
- ECG
- Echocardiography
- Blood analyses
- Chest X-ray

Extensive Inflammatory Features
Acute Pericarditis

Pericardial LGE

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1. **Infectious etiology**

i. Identification of viral genome by PCR in 1/3 of recurrent pericarditis cases, either in the effusion or in epicardial biopsy specimens.

2. **Autoimmune mechanism**

It is believed to be involved in 2/3 of recurrent pericarditis cases. It is supported by the following findings:

i. presence of a latent period of several weeks,

ii. presence of autoantibodies in the sera of patients (67% anticardiac - 48% antinuclear),

iii. responsiveness to anti-inflammatory therapies,

iv. association with other autoimmune processes,

v. familial occurrence of recurrences in up to 10% of patients,


The Role of the Immunogenetic Background in the Development and Recurrence of Acute Idiopathic Pericarditis

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Fig. 1. Statistically significant differences in HLA allele frequencies between healthy controls and patients with AIP (a) and RP (b).
3. Autoinflammatory mechanism

- Autoinflammatory diseases include those genetic disorders characterized by primary dysfunction of the innate immune system.
- They 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 - accounts for ~6% or recurrent pericarditis cases).

4. Apart from the latter mechanisms in some cases, recurrences may be promoted by inappropriate use of medical therapies:

i. Early use of steroids may facilitate viral replication and disease recurrence.

ii. Fast tapering or discontinuation of anti-inflammatory therapy, before complete symptoms remission and CRP normalization, may promote recurrences as well.

Physical activity in patients with IRP must be limited until the complete remission of fever and chest pain.

A minimal restriction of 3 months has been arbitrarily defined according to expert consensus.

Athletes are recommended to return to competitive sports only after symptoms have resolved and diagnostic tests (i.e. CRP, ECG, and echocardiogram) have been normalized.
Clinical poor prognostic predictors for pericarditis with need for hospitalization

Baseline features associated with a specific (secondary cause)
- Fever > 38°C
- Subacute onset
- Large pericardial effusion
- Cardiac tamponade
- Lack of response to aspirin or NSAIDs after at least 1 week of therapy

Baseline features associated with complicated in-hospital course
- Myopericarditis
- Immunodepression
- Trauma
- Oral anticoagulant therapy

Lange RA et al. NEJM 2004;351:2195-2202.
Dose tapering should be not be performed before clinical remission and CRP normalization.

Conclusions: hs-CRP is elevated at week 1 of acute idiopathic pericarditis, identifies patients at higher risk of recurrence, and could be used to monitor disease activity and select appropriate therapy length.
The primary outcome occurred in 20 patients (16.7%) in the colchicine group and 45 patients (37.5%) in the placebo group (relative risk reduction in the colchicine group, 0.56, confidence interval, 0.30 to 0.72; number needed to treat, 4; p<0.001).
Colchicine in patients with multiple recurrences

Colchicine halved the number of recurrences (21.6% vs 42.5% - RR=0.49 - NTT=5) in patients with multiple recurrences (≥2).

According to the current guidelines in patients with a poor general condition, in cases of NSAIDs failure, and in frequent, hard-to-control recurrences (Class IIa C)

The guidelines recommend a dose of 1-1.5 mg/Kgr prednisone for at least 1 month, tapered over a three-month period.
- 100 patients with recurrent pericarditis
- Half of the patients were given low doses of prednisone (0.2-0.5 mg/kg/day), while the others received a high dose (1 mg/kg/day).

- It was also found a lower incidence of adverse effects in the low dose regimen (23.5% vs. 2%, p=0.002).

Resistant idiopathic recurrent pericarditis (or colchicine-resistant steroid-dependent cases)

- This definition should apply to cases with hard-to-control chest pain and multiple recurrences that require high doses of corticosteroids (namely prednisone >12.5mg daily) for long periods to be controlled.
- They probably represent 5-10% of recurrent cases.
- They should be addressed to specialized centers.

i. Use of drug combinations

- Combinations should include 3 drugs and specifically aspirin or an NSAID in the recommended doses, colchicine and corticosteroids.

- In patients with multiple recurrences very slow tapering of steroids should be considered.

- During the tapering process at the critical threshold dose of steroids for recurrences, adding aspirin-NSAID to colchicine plus corticosteroid is recommended, in an effort to avoid an increase in the dosage of steroids.

ii. Classic Immunosuppressive drugs

- They have a delayed onset of action (2-6 weeks).
- Less toxic and less expensive drugs (such as azathioprine or methotrexate) should be preferred.
- Azathoprine at a dose of 1.5-2.5mg/kg/daily is the most used medication.

Azathioprine in isolated recurrent pericarditis: A single centre experience

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- This is the largest published series on the treatment of recurrent pericarditis with immunosuppressants and specifically with azathioprine
- 46 patients with ≥2 recurrences, aged ~40±17 years, 22 males, mean follow-up ~61 months.

Azathioprine was administered at the dose of 1.5-2.5 mg/kg

<table>
<thead>
<tr>
<th>Clinical features of patients.</th>
<th>n.</th>
<th>M/F</th>
<th>Previous therapy</th>
<th>Total recurrences before AZA (mean/patient)</th>
<th>Duration of AZA average ± SD</th>
<th>Total recurrences with AZA (mean/patient)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>40</td>
<td>20/20</td>
<td>P/F (16) P/F/C (19) P/Cy/M/Cx (2) P/Cy/M/Cy (1) P/Cy (1) P/Cx/PPW (1) P/F (3) P/F/C (3)</td>
<td>148 (3.5)</td>
<td>13.6 ± 5.1</td>
<td>39 (2.4)</td>
</tr>
<tr>
<td>Post-IMA, Post-pericardiomy or Post-traumatic</td>
<td>6</td>
<td>2/4</td>
<td>P/F (3) P/F/C (3)</td>
<td>17 (2.8)</td>
<td>11.5 ± 2.8</td>
<td>0</td>
</tr>
</tbody>
</table>

AZA: azathioprine; P: prednisone; F: FANS; C: colchicine; M: methotrexate; Cy: cyclosporine; Cx: cyclophosphamide; PPW: pleuro-pericardial window.
The relative Risk (RR) of recurrence of pericarditis in patients receiving azathioprine was 0.34 (p<0.0001).

- In all the 39 (84.7%) responding patients, steroids were successfully discontinued between 4 and 12 months from the beginning of azathioprine therapy.
- Discontinuation of azathioprine without recurrence was observed in 27 cases (58.6%).
Overall azathioprine was well tolerated in this series. Slight and transient hepatotoxicity was observed in 5 patients (10.8%) and leucopenia in 3 patients (6.5%).
iii. Anakinra

Rationale for anakinra administration:

- Idiopathic recurrent pericarditis shares several features with autoinflammatory diseases and at least in some cases, it is believed that autoinflammation constitutes the underlying pathogenetic mechanism.

- Anakinra is an interleukin-1 (IL-1b) receptor antagonist and autoinflammatory diseases have shown a favorable response to interleukin-1 (IL-1) inhibition.

Mechanism of action of anakinra

IL-1=Interleukin-1
IL-1RI=Interleukin-1 receptor type I
IL-1 Ra= Interleukin-1 receptor antagonist

Fifteen patients (12 children, 3 adults), multicenter retrospective study.

Anakinra was proved a rapidly acting, highly effective and safe overall agent but...
Systematic review of published cases with anakinra (AN) administration in idiopathic recurrent pericarditis

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<thead>
<tr>
<th>Treatment protocol</th>
<th>100mg sc daily for at least 6months</th>
</tr>
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<tbody>
<tr>
<td><strong>Total number of patients</strong></td>
<td><em>34 (20 males)</em></td>
</tr>
<tr>
<td><strong>Disease duration</strong></td>
<td>16 months</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>26 months</td>
</tr>
<tr>
<td><strong>Number of recurrences before AN</strong></td>
<td>6</td>
</tr>
<tr>
<td><strong>Time to steroids withdrawal</strong></td>
<td>30days*</td>
</tr>
<tr>
<td><strong>Time to CRP normalization</strong></td>
<td>7 days</td>
</tr>
<tr>
<td><strong>REC during full-dose AN</strong></td>
<td>0%</td>
</tr>
<tr>
<td><strong>REC after drug discontinuation</strong></td>
<td>~75%</td>
</tr>
<tr>
<td><strong>Time to REC</strong></td>
<td>15 days</td>
</tr>
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</table>

*Data are presented as median values.

Intravenous human immunoglobulins

Mechanism of action of IvIg

Treatment protocol
400 to 500 mg iv daily for 5 consecutive days with 1 cycle 1 month later in cases of incomplete remission.

# Systematic review of published cases with IVIG administration in recurrent pericarditis

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<td><strong>Follow-up</strong></td>
<td>19.5 months</td>
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<tr>
<td><strong>Disease duration</strong></td>
<td>315 days</td>
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<tr>
<td><strong>Number of recurrences before IVIG</strong></td>
<td>3</td>
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<tr>
<td><strong>Time to steroids withdrawal (months)</strong></td>
<td><em>5.7 (16.6% are still on steroids)</em></td>
</tr>
<tr>
<td><strong>Time to REC</strong></td>
<td>5 months</td>
</tr>
<tr>
<td><strong>Pts free of recurrences</strong></td>
<td>73.3%</td>
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If pericarditis is associated with a known disease*, treatment of the underlying disease through a multidisciplinary approach is of paramount importance.

* Uremia
  * Tuberculosis
  * Neoplasm
  * Autoimmune or inflammatory disease
  * Myocardial infarction
  * Postcardiotomy syndrome
  * Trauma
  * Aortic dissection
  * Endocrine disorders
  * Chest wall irradiation
  * Adverse drug reaction-toxins
v. Pericardiectomy

- Pericardiectomy should be reserved only for frequent, strongly symptomatic recurrences (especially recurrent tamponade) resistant to medication.
- Referral of these patients to centers with specific expertise in this surgery is recommended.
- During surgery every effort should be made to remove the complete pericardium.

- In a retrospective study in 184 pts (1994-2005) pericardiectomy was very effective in reducing the rate of recurrences with a perioperative mortality of 0% and rate of major complications 3%.

Prognosis

- The in-hospital mortality of acute pericarditis is estimated at 1.1%
- Prognosis is excellent in idiopathic pericarditis and depends on the underlying condition in the secondary forms.
- Complications include recurrent pericarditis, cardiac tamponade and permanent constrictive pericarditis.

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61 patients who were referred to a tertiary hospital for resistant idiopathic recurrent pericarditis were followed for an average of 8.3 years:

- During follow-up in 70% of cases pericarditis remained idiopathic, whereas a new diagnosis of systemic inflammatory disease (namely rheumatoid arthritis and Sjogren's syndrome), emerged in the rest.

**Key message**

Idiopathic recurrent pericarditis is not necessarily a life-long diagnosis
Thank you for your attention