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1 **Acute recurrent pericarditis: from pathophysiology toward new treatment**
2 **strategy**

3

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31 Abstract

32 Acute idiopathic or so-called “viral” pericarditis is a frequent and usually benign
33 disease, although recurrences are frequent. Data strongly suggest the presence of
34 underlying auto-inflammatory and/or auto-immune disorders. It has been reported an
35 inflammatory response of the innate immune system typical of “auto-inflammatory diseases”,
36 predominantly mediated by interleukin-1 [IL-1]. This may result from the activation of the
37 inflammasome by a cardiotropic virus or a nonspecific agent. The inflammatory response of
38 the adaptive immune system, typical of “auto-immune diseases” - mainly mediated by
39 autoantibodies or autoreactive T lymphocytes - seems also involved as anti-heart or anti-
40 intercalated disk autoantibodies were associated with a higher number of recurrences and
41 hospitalizations. Current guidelines recommend that aspirin/non-steroid anti-inflammatory
42 drugs (NSAIDs) for a few weeks should be associated to colchicine for 6 months in recurrent
43 pericarditis. In refractory cases, low dose corticosteroids or immunosuppressive drugs have
44 been proposed with limited efficacy. Growing evidences suggest a place of IL-1 receptor
45 antagonists in the treatment of recurrent pericarditis. Many retrospective studies, one recent
46 randomized placebo controlled study and data of a real life large international registry
47 showed the good efficacy of anakinra with a good safety profile. Other IL-1 receptor
48 antagonists showed promising results (canakinumab, rilonacept). However, IL-1 receptor
49 antagonists position in the treatment algorithm of recurrent pericarditis needs further
50 evaluation in larger prospective clinical trials to replicate initial findings as well as to assess
51 safety, cost-effectiveness and long-term efficacy.

52

53

54 **Key words:** recurrent pericarditis; autoinflammatory; autoimmune; treatment; interleukin 1

55 **Background**

56 Acute pericarditis is a frequent and usually benign disease characterized by chest
57 pain, pericardial friction rub, widespread saddle-shaped or concave upward ST segment
58 elevation on the electrocardiogram (ECG), and pericardial effusion [1]. Diagnostic evaluation
59 include auscultation, electrocardiogram, echocardiography, biomarkers of inflammation (C-
60 reactive protein [CRP]) and myocardial lesion (troponin), and chest X-ray. The major causes
61 of pericarditis are summarized in **Table 1**. In developed countries, idiopathic or so-called
62 “viral” pericarditis is the commonest final diagnosis [2,3,4]. In a biopsy study including 259
63 patients with a large pericardial effusion, the underlying cause was identified by molecular
64 and immune-histological methods mainly as autoreactive/lymphocytic (i.e. idiopathic or
65 “viral”, 35%), malignant (28%), traumatic (i.e. post-cardiac surgery, 15%), and viral (12%) [5].
66 The etiologic spectrum is different in developing countries, with a high prevalence of
67 tuberculosis (70% of pericarditis in sub-Saharan Africa, and $\geq 90\%$ when associated with HIV
68 infection). Some features have proved to be independent predictors of a specific cause (non-
69 viral or non-idiopathic pericarditis), i.e. fever $>38^{\circ}\text{C}$ (hazard ratio [HR], 3.56), subacute
70 course (HR, 3.97), large pericardial effusion or cardiac tamponade (HR, 2.15), and failure of
71 non-steroid anti-inflammatory drugs (NSAIDs)(HR, 2.50) [6,7,8,9].

72 After the first episode of acute pericarditis, recurrences are frequent (20 to 50%).
73 Recurrent pericarditis is defined as a recurrence of chest pain associated with at least one of
74 the following objective evidence of disease activity: fever, pericardial rub, ECG changes, new
75 or worsening pericardial effusion and/or elevation of biomarkers of inflammation (elevation in
76 white blood cell count, erythrocyte sedimentation rate, or CRP) after a free interval of 4-6
77 weeks following the first episode (**Figure 1**). These criteria, although arbitrary, are generally
78 accepted.

79 The pathogenesis of recurrent pericarditis has long been poorly understood. Recent
80 data strongly suggest underlying auto-inflammatory and/or auto-immune disorders, with viral
81 infections as possible triggers (**Figure 2**). On the one hand, the inflammatory response of the
82 innate immune system typical of “auto-inflammatory diseases” - predominantly mediated by

83 cytokines (mainly interleukin-1 [IL-1]) - has been reported in patients with recurrent
84 pericarditis [10,11]. Conversely, auto-inflammatory diseases such as cryopyrin-associated
85 periodic syndromes and familial Mediterranean fever (FMF) are characterized by
86 spontaneous onset of intermittent inflammatory attacks with fever and serositis frequently
87 including pericarditis [12,13,14,15]. In recurrent pericarditis, the auto-inflammatory
88 mechanism may result from activation of the inflammasome by a cardiotropic virus or a
89 nonspecific agent in a patient who has abnormal innate immunity. This will cause release of
90 pro-inflammatory cytokines including interleukins - mainly IL-1 - that bring neutrophils and
91 macrophages to the injured area [16]. Of note, colchicine is able to modulate innate immunity
92 and to block the processing of IL-1 β . Its efficacy in the treatment of FMF relapses is largely
93 proved, as well as in the reduction of pericarditis recurrences [2,3,7]. More recently, anakinra
94 - a short-acting IL-1 receptor antagonist - has shown good results in controlling very quickly
95 the acute attack and decreasing relapses in idiopathic recurrent pericarditis. On the other
96 hand, the inflammatory response of the adaptive immune system, typical of "auto-immune
97 diseases" - mainly mediated by autoantibodies or autoreactive T lymphocytes [9] - also
98 seems to be involved in idiopathic recurrent pericarditis. Anti-heart autoantibodies (AHA) or
99 anti-intercalated disk autoantibodies (AIDA) have been found in adult cases and were
100 associated with a higher number of recurrences and hospitalizations [17].

101 Recurrent acute attacks of pericarditis have a negative impact on morbidity and
102 quality of life of patients. The presence of large effusion and tamponade (HR, 2.51) and
103 NSAIDs failure (HR, 5.50) identify increased risk of complications during follow-up [6].
104 However, the overall long-term prognosis of idiopathic recurrent cases is very good. The
105 most serious risk - the risk of pericardial constriction - has been estimated to be below 1%
106 among 500 patients, after a median follow-up of 72 months [18,19,20].

107

108 **Treatment**

109 The treatment of first episode of recurrent pericarditis is quite similar to the treatment
110 of the initial episode of acute pericarditis. In the presence of multiple recurrences, other

111 therapeutic options should be discussed (all therapeutic options are summarized in **Figure**
112 **3**). Of course, in the event of an underlying etiology identified and for which therapeutic
113 options are available (i.e. curable infectious diseases, cancers, systemic diseases...), the
114 treatment of such causal disease is of major importance. Physical activity may have a role in
115 the recurrence and exacerbation of pericarditis. A moderate restriction of physical activity up
116 to what is necessary to perform domestic tasks and undertake sedentary work is generally
117 advised [21].

118 ***Colchicine and NSAIDs***

119 For the treatment of acute pericarditis, aspirin and NSAIDs are mainstays and should
120 be used at full anti-inflammatory doses until symptoms disappear and CRP completely
121 normalizes [2,4,22]. First evidence-based to support the use of colchicine came from open
122 label trials. The COlchicine for PEricarditis (COPE) trial included 120 patients with a first
123 episode of acute pericarditis [23]. Colchicine for three months on top of aspirin or NSAIDs
124 decreased the recurrence rate and symptom persistence at 72 hours. In a multicentre,
125 double blind trial [Investigation on Colchicine for Acute Pericarditis (ICAP)], two hundred and
126 forty adults with acute pericarditis were randomly assigned to receive for three months either
127 colchicine or placebo, in addition to NSAIDs [24]. Incessant or recurrent pericarditis occurred
128 less frequently in the colchicine versus the placebo group (16.7 % vs. 37.5 %; $P<0.001$).
129 Colchicine significantly reduced the rate of symptom persistence at 72 hours, the remission
130 rate at one week, the number of recurrences per patient, and the hospitalization rate.

131 For the treatment of patients with one or two recurrences of pericarditis, preliminary
132 evidence for the use of colchicine came from non-randomized studies. The COlchicine for
133 Recurrent Pericarditis (CORE) trial included eighty-four patients with recurrent pericarditis
134 [25]. Colchicine plus aspirin or NSAIDs for six months decreased the recurrence rate of
135 pericarditis at 18 months (24.0% vs. 50.6%; $P<0.022$). A prospective, randomized, double
136 blind, placebo-controlled multicenter trial [Colchicine for Recurrent Pericarditis (CORP)] [26],
137 demonstrated the efficacy of colchicine in 120 patients with a first recurrence of pericarditis.

138 For patients with multiple (≥ 2) pericarditis recurrences, another multicenter, double-
139 blind randomized trial evaluated the efficacy of colchicine for six months in addition to
140 NSAIDs [Colchicine for Recurrent Pericarditis 2 (CORP-2)] [27]. The relative risk reduction of
141 recurrent pericarditis in the colchicine vs. the placebo group was 0.49 (95% CI 0.24-0.65).
142 Colchicine significantly reduced the rate of symptom persistence at 72 hours, the number of
143 recurrences per patient, and the hospitalization rate and increased the remission rate at one
144 week. Of note, adverse effects and rates of study-drug discontinuation were similar in the two
145 study groups.

146 ***Corticosteroids or immunosuppressive agents***

147 There is still controversy to know if (and when) corticosteroids or immunosuppressive
148 agents should be considered for recurrent pericarditis [2]. Studies have shown that
149 corticosteroids could increase the rate of recurrence [28,29]. High dose of steroids should be
150 avoided as they proved to have less benefit and higher risk of corticosteroid-dependence
151 than low doses [29]. A recent report showed that in patients with idiopathic pericarditis
152 recurrences despite a well conducted treatment with aspirin or NSAIDs and colchicine,
153 steroids or immunosuppressive agent (azathioprine, methotrexate, and mycophenolate
154 mofetil) may help to control the disease [30]. The mean frequency per month (\pm SD) of
155 pericarditis recurrences was 0.69 (\pm 0.40) with aspirin/NSAIDs and colchicine, 0.22 (\pm 0.34)
156 with corticosteroids alone and 0.01 (\pm 0.04) with immunosuppressive agents ($p < 0.001$).
157 Current guidelines favor the addition of corticosteroids at low to moderate doses (i.e.
158 prednisone 0.2–0.5 mg/kg/day) in cases of incomplete response or recurrences on
159 aspirin/NSAIDs and colchicine. Two recent systematic reviews described the existing
160 evidence for immunosuppressive drugs in idiopathic refractory recurrent pericarditis [7,31]. In
161 the largest reported experience, azathioprine was administered at a dose of 1.5–2.5
162 mg/kg/day for 13.6 ± 5.1 months in forty-five patients [32]. It was associated with remission
163 after steroid discontinuation in more than fifty percent of patients and well tolerated.

164 Intravenous immunoglobulins have been proposed in refractory cases [33,34]. High
165 dose intravenous immunoglobulins associated to NSAIDs, steroids, or colchicine treatment

166 have been used for 11 months in nine patients with recurrent pericarditis (mean of 5 relapses
167 per patient) [33]. Patients showed complete clinical remission with no further relapse after
168 one or two intravenous immunoglobulins session (n=6), a single minor relapse responsive to
169 short-term NSAIDs (n=2), and no response (n=1).

170 ***The era of interleukin-1 receptor antagonist***

171 There is accumulating evidences of effectiveness of anti-IL1 agents. Three molecules
172 are available. Anakinra is a recombinant form of the IL-1 antagonist receptor (IL-1Ra).
173 Riloncept, a dimeric fusion protein blocking IL-1, contains the extracellular parts of the IL-1
174 receptors (IL-1R1 and IL-1RAcP). Canakinumab is a humanized antibody that prevents IL-1 β
175 from binding to its receptor.

176 Anakinra has first shown its effectiveness in pediatric recurrent pericarditis [35,36]
177 (**Table 2**). In a retrospective study, corticosteroid-dependent patients received anakinra 1 to
178 2 mg/kg/d [36]. All patients showed a complete response within a few days and were able to
179 rapidly withdraw corticosteroids. During anakinra tapering, 6 out of 14 patients experienced a
180 relapse, with a prompt response after anakinra reintroduction. After a mean follow-up of 39
181 months, authors reported a 95% reduction of pericarditis flares vs. pre-treatment period. Ten
182 adult patients with idiopathic recurrent pericarditis treated with anakinra were analyzed [37].
183 All patients were resistant and/or intolerant to previous treatment with NSAIDs, colchicine
184 and corticosteroids, while two had failed also azathioprine therapy. The mean number of
185 recurrences was 8, the mean baseline dose of prednisolone was 14.1 mg/day and the mean
186 baseline CRP level was 74 mg/dL. Patients were given daily subcutaneous anakinra (100
187 mg) for six months followed by alternate day dosing for another six months. Anakinra was
188 highly effective in all cases leading to rapid symptom relief (within 2 days), CRP
189 normalization (5.9 days) and tapering/discontinuation of corticosteroids (37.5 days). Five out
190 of 7 patients relapsed shortly after anakinra discontinuation and in 4 out of 5 patients
191 anakinra was re-started with immediate control of symptoms. Side effects included minor
192 local reactions at the injection site and transient transaminasemia. In a retrospective study
193 from the Mayo clinic, thirteen patients with treatment-refractory recurrent idiopathic

194 pericarditis for a mean duration of 3 years (1.1 to 6.0) received anakinra [38]. Response to
195 therapy was rapid (2 to 5 days) and included complete (n=12) or partial (n=1) resolution of
196 symptoms. At last follow up, 11 out of 13 patients discontinued NSAIDs, colchicine, and
197 glucocorticoids, 2 stopped anakinra without flare, and 11 patients remained on anakinra. The
198 experience of the NIH was recently reported [39]. A series of 10 patients had recurrent
199 idiopathic pericarditis refractory to NSAIDs, colchicine and steroids (n=10), and
200 immunosuppressant (n=6). After patients received anakinra (100 or 200 mg/day) for a mean
201 duration of 26.5 months (11.5-66.8), they showed a complete response (n=5), a partial
202 response (n=4), and no response (n=1). In their review, Lazaros et al [40] analyzed nine
203 reports (34 patients, 20 men, mean age 26.8 years) of anakinra in patients with idiopathic
204 recurrent pericarditis. The mean disease duration was 31 months and the mean number of
205 recurrences 8.2. Anakinra was administered as a daily subcutaneous injection of 100 mg or a
206 mean dose of 1.1 mg/kg/d in weight-adjusted regimens. The mean full-dose duration was 9.2
207 months. CRP normalized within 7.1 days, and steroids were withdrawn within 62 days. Dose
208 tapering was adopted in 65% of patients, leading to recurrence in 26% of cases. After a
209 mean of 28.3 months follow-up, eight out of 34 (23.5%) patients were disease free without
210 treatment, after having received anakinra for 10.4 months overall. Mild local reaction were
211 reported in 44% of patients.

212 Recently, a double blind, placebo-controlled, randomized trial was conducted among
213 twenty-one patients who presented three or more previous recurrences of pericarditis,
214 colchicine resistance, and corticosteroid dependence [Anakinra Treatment of Recurrent
215 Idiopathic Pericarditis (AIRTRIP)] [41]. In a first phase, anakinra was administered to all
216 patients at 2 mg/kg per day, up to 100 mg, for two months; then patients who responded with
217 resolution of pericarditis were randomized to continue anakinra (n = 11) or switch to placebo
218 (n = 10) for six months or until a pericarditis recurrence. Recurrent pericarditis occurred in 9
219 of 10 patients (90%; incidence rate, 2.06% of patients per year) assigned to placebo and 2 of
220 11 patients (18.2%; incidence rate, 0.11% of patients per year) assigned to anakinra. Median
221 flare-free survival after randomization was 72 days in the placebo group and not reached in

222 the anakinra group ($P < 0.001$). During anakinra treatment, 95.2% of patients experienced
223 transient local skin reactions, 4.8% herpes zoster, 14.3% transaminase elevation, and 4.8%
224 ischemic optic neuropathy. No adverse events occurred during placebo treatment. Data of a
225 large international multicenter registry of anakinra in the treatment of recurrent pericarditis
226 were recently published [42]. A total of 224 patients (46 years old, 63% women, 75%
227 idiopathic) with recurrent pericarditis for 17 months who were corticosteroid dependent and
228 colchicine resistant and treated with anakinra were included. Most patients had elevated
229 CRP (91%) and pericardial effusion (88%). After a median anakinra (100 mg per day
230 subcutaneously) treatment of 6 months, pericarditis recurrences were reduced six-fold (2.33-
231 0.39 per patient per year), emergency department admissions 11-fold (1.08-0.10 per patient
232 per year), and hospitalizations seven-fold (0.99-0.13 per patient per year). Corticosteroid use
233 was decreased from 80% to 27%. Adverse events consisted mostly of transient skin
234 reactions (38%) at the injection site, which led to anakinra discontinuation in only 3%. A full-
235 dose anakinra duration of over 3 months followed by a tapering period of over 3 months were
236 the therapeutic schemes associated with a lower risk of recurrence.

237 Finally, in a recent multicenter phase II clinical trial, rilonacept has been used in
238 twenty-five symptomatic or corticosteroid dependent patients with idiopathic or post-
239 pericardiotomy recurrent pericarditis. Twenty-three patients completed 6 months of rilonacept
240 treatment, 160 mg SC weekly after a 320 mg load dose, with a good efficacy on pain and
241 CRP levels [43].

242 Of note, anti-IL1 agents must be used taking into account possible contraindications,
243 infectious diseases or underlying immunosuppression, and the risk of infection. Anakinra is
244 contraindicated in kidney failure. The therapeutic choice must also take into account the cost
245 of such molecules, particularly for canakinumab.

246 **Remaining challenges**

247 Although major advances have been done during the last decade, there remain some
248 issues in the care of patients with recurrent pericarditis. What is the best length of colchicine
249 treatment for acute or recurrent pericarditis? Current guidelines suggest a duration of

250 treatment with colchicine of 3 months in the first acute episode and 6 months in recurrent
251 pericarditis. In recurrent more severe cases, considering the good tolerance, a longer use of
252 the colchicine up to 12 to 24 months, tailored to the individual patient and with gradual
253 tapering, may be useful [4]. The dose and duration of NSAIDs treatment are still debatable
254 as well as the need for gradual tapering. What is the efficacy and safety of colchicine in non-
255 viral/non-idiopathic pericarditis ? The Colchicine for the Prevention of the Post-
256 pericardiotomy Syndrome (COPPS and COPPS2) trials published in 2011 and 2014 showed
257 efficiency of colchicine on preventing post-pericardiotomy syndrome but not of postoperative
258 atrial fibrillation or postoperative pericardial/pleural effusion. Colchicine treatment was
259 associated with a higher rate of digestive side effects. The efficacy and safety of colchicine in
260 systemic autoimmune diseases remains unknown [44,45]. How to manage patients with
261 recurrent pericarditis and corticosteroid dependence? Although growing evidence suggests a
262 place of IL-1 receptor antagonists (anakinra, canakinumab, rilonacept), their position in the
263 treatment algorithm of recurrent pericarditis needs further evaluation in larger prospective
264 clinical trials to replicate initial findings as well as to assess safety, cost-effectiveness and
265 long-term efficacy.

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443 **Table 1. Major causes of pericarditis.**

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Idiopathic
Malignancy
Post-Cardiac injury syndrome Post-myocardial infarction Post-pericardiotomy Post-traumatic
Infectious diseases Viral, including HIV Bacterial and mycobacterial Fungal
Radiation
Systemic disorders Connective tissue diseases Systemic lupus erythematosus Rheumatoid arthritis Systemic sclerosis Sjögren's syndrome Myositis Granulomatous diseases Sarcoidosis Vasculitis Behçet syndrome Small vessels : eosinophilic granulomatosis with polyangiitis, granulomatosis with polyangiitis Medium-sized vessels : polyarteritis nodosa, Kawasaki disease Auto-inflammatory diseases Familial Mediterranean Fever (FMF) Tumor necrosis factor receptor-1 associated periodic syndrome (TRAPS)

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447 **Table 2: Series of anakinra use in recurrent pericarditis.**

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Reference, year	Methods	Patient number	Resistance to treatment	Anakinra dose	Complete response	Partial response	Pericarditis relapse after anakinra withdrawal
34, 2014	Retrospective cohort	14	CS	1-2 mg/kg/d	100%	0%	43%
35, 2014	Retrospective cohort	10	NSAIDs, CS, colchicine, azathioprine	100 mg/d	70%	30%	71%
36, 2015	Retrospective cohort	13	NSAIDs, CS, colchicine	100 mg/d	92%	8%	NA
38, 2016	Literature review	34	NSAIDs, CS, colchicine	100 mg/d or 1.1 mg/kg/d			
39, 2016	Prospective, double blind, placebo controlled	21	NSAIDs, CS, colchicine	2 mg/kg/d up to 100 mg/d	100% under anakinra open label phase	0%	90% placebo group vs. 18% anakinra group during double blind phase
37, 2018	Retrospective cohort	10	NSAIDs, CS, colchicine, IS	100-200 mg/d	50%	40%	NA
42, 2019	Prospective international registry	224	NSAIDs, CS, colchicine	100 mg/d	43%	29%	2.33 to 0.39 per patient/yr

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451 NSAIDs, non-steroid anti-inflammatory drug; NA, not available

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Figure 1. Recurrent pericarditis diagnosis flowchart.

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Figure 2. Schematic of the pathogenesis of recurrent pericarditis and impact of main treatment used.

459 After pericardial damage (viral, traumatic...), two separate pathways of immunity may be
460 activated. From innate immunity, a group of pattern recognition receptors (TLR and NLR) will
461 assemble and oligomerize into the inflammasome, an activating structure of caspase 1. This
462 will lead to the production of inflammatory cytokines including IL1 β , which will cause the
463 production of cyclooxygenase (COX) resulting in the production of prostaglandins. At the
464 same time, an involvement of the adaptive immune system has been proposed via the
465 production of anti-heart (AHA) and anti-intercalated disk antibodies (AIDA), produced by
466 lymphocytes activated by antigen-presenting cells (having encountered pericardial antigens
467 released after the pericardial lesion). These lymphocytes also produce inflammatory
468 cytokines such as IL6, IL8 and IFN γ . Corticosteroids will have an impact on both sides
469 of the immune system, innate and adaptive. Other treatments currently used in recurrent
470 pericarditis have an impact on innate immunity: colchicine inhibits the action of the
471 inflammasome, anti-IL1 agents counter the inflammatory activity of IL1 and NSAIDs inhibit
472 COX.

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AHA, anti-heart antibodies; AIDA, anti-intercalated-disk autoantibodies; DAMPs, damage-associated molecular patterns; NLR, nod-like receptor; NSAIDs, nonsteroidal anti-inflammatory drugs; PAMPs, pathogens-associated molecular patterns; TLR: toll-like receptor

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Figure 3. Recurrent pericarditis therapeutic options flowchart.

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