State of the Art in Pericarditis Treatment

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What we are going to talk about…

1. Diagnostic criteria
2. Etiology
3. Anti-inflammatory therapy-NSAIDs
4. Colchicine
5. Corticosteroids
6. New therapies and prognosis

Diagnostic Criteria for Pericarditis

Pericarditis	Definition and diagnostic criteria
Acute	Inflammatory pericardial syndrome to be diagnosed with at least 2 of the 4 following criteria: 1. Pericarditic chest pain 2. Pericardial rubs 3. New widespread ST elevation or PR depression on ECG 4. Pericardial effusion (new or worsening) Additional supporting findings: Elevation of markers of inflammation (i.e. C-reactive protein, erythrocyte sedimentation rate and white blood cell count) Evidence of pericardial inflammation by an imaging technique (computed tomography, cardiac magnetic resonance)

Classical clinical criteria

Biomarkers

Imaging to evaluate pericardial inflammation

RECURRENT PERICARDITIS IF A SYMPTOM FREE INTERVAL > 4-6 weeks

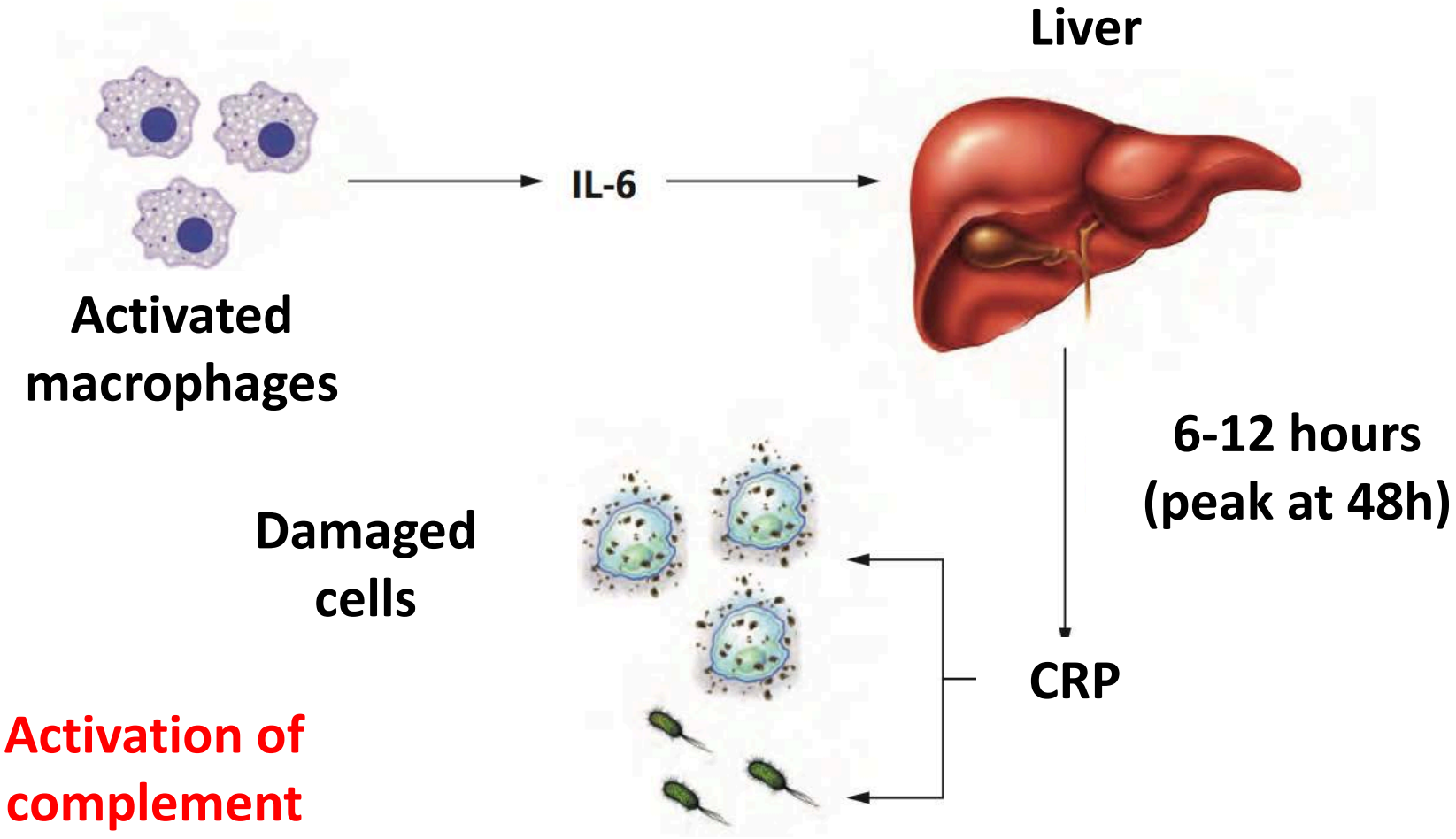
Or

INCESSANT PERICARDITIS IF SYMPTOM FREE TIME < 4-6 weeks

Higher risk of constriction?

2015 ESC guidelines criteria; Table from Imazio M. Myopericardial Diseases Springer 2016

C-reactive protein and pericarditis (80% of cases at presentation)

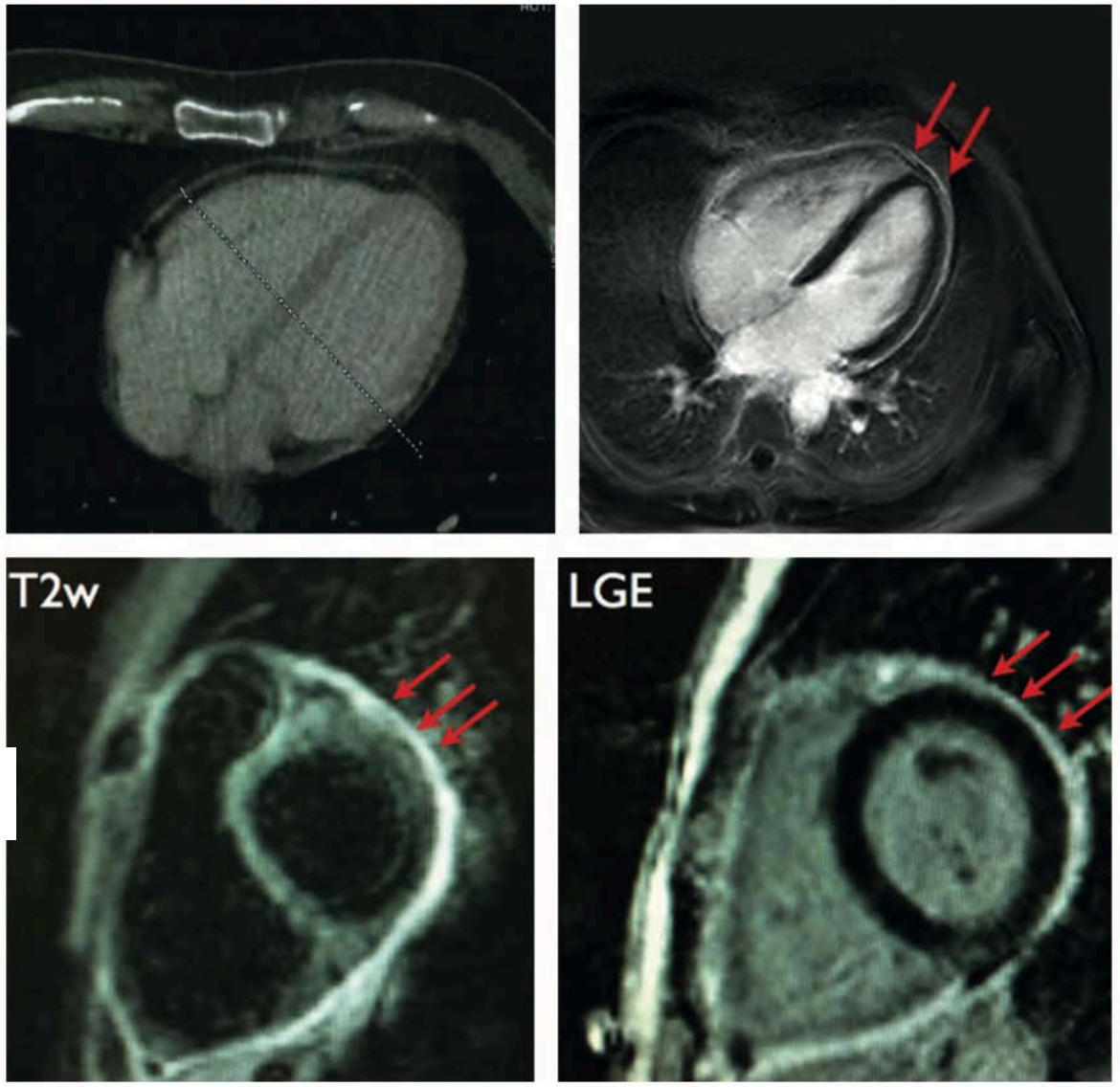


Imazio M. Le Malattie del Pericardio. Pensiero Scientifico Editore 2016

Imaging (CT and CMR) to evaluate pericardial and myocardial inflammation

CT

CMR



First-line anti-inflammatory therapy: Aspirin or NSAID plus colchicine (Rec. IA)

1. Proper dosing and times
2. Add colchicine on top
3. Consider tapering

Drug	Usual dosing	Duration	Tapering
Aspirin	750–1000 mg every 8 h	1–2 weeks	Decrease doses every week, e.g. 750 mg TID for 1 week, then 500 mg TID for 1 week then stop
Ibuprofen	600 mg every 8 h	1–2 weeks	Decrease doses every week, e.g. 600 mg plus 400 mg plus 600 mg for 1 week, then 600 mg plus 400 mg plus 400 mg for 1 week, then 400 mg TID for 1 week then stop
Colchicine	0.5 mg once (<70 kg) or 0.5 mg BID (≥70 kg)	3 months Acute 6 months Recurrent	Not mandatory, alternatively 0.5 mg every other day (<70 kg) or 0.5 mg once (≥70 kg) in the last weeks

Therapy duration is individualized when guided by symptoms and CRP normalization: keep the attack dose and taper only if asymptomatic and CRP is normalized (Class IIa recommendation, LOE B)

Colchicine: Class I indication(LOE A)

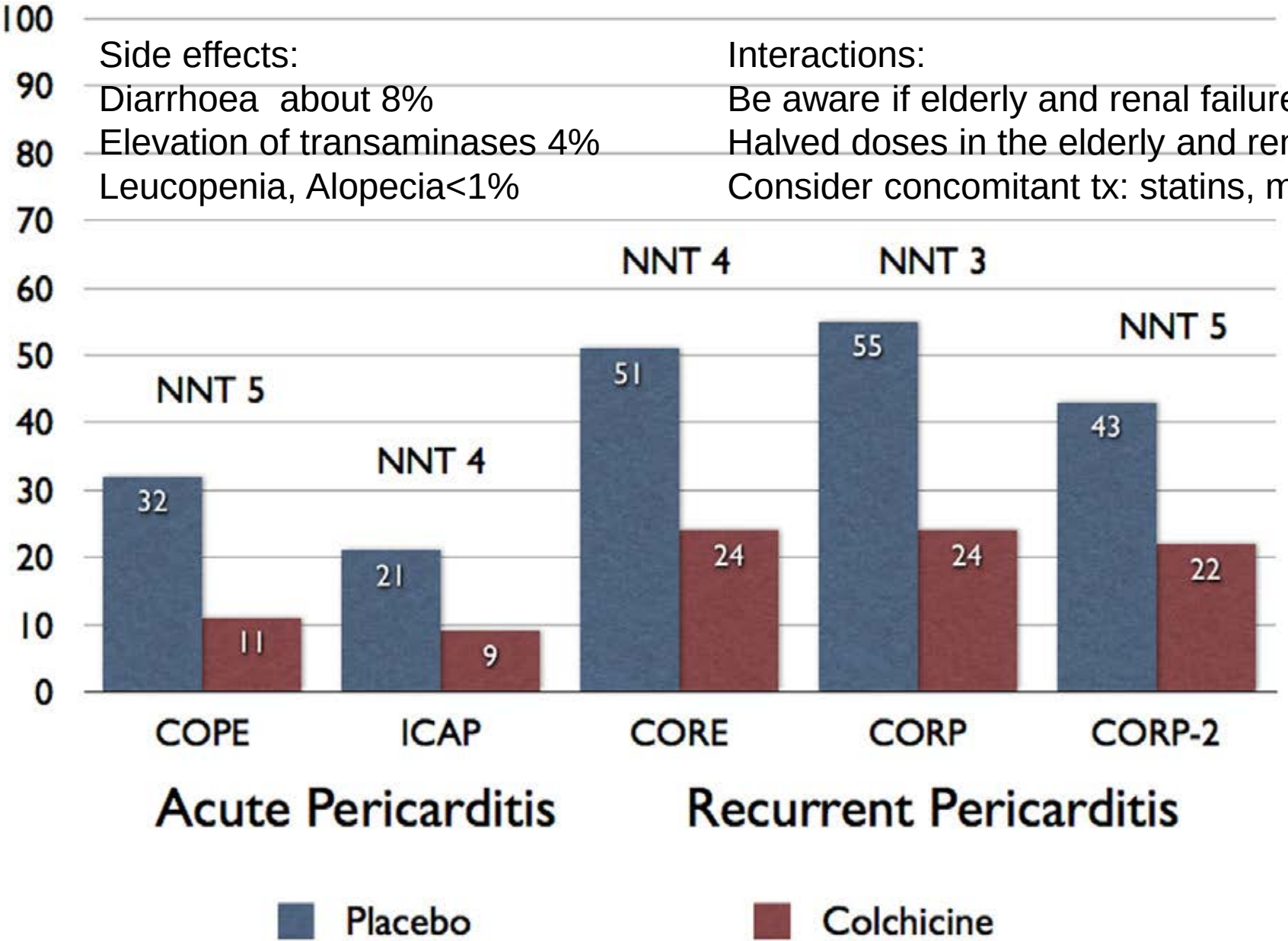
Recurrence Frequence at 18 months

%

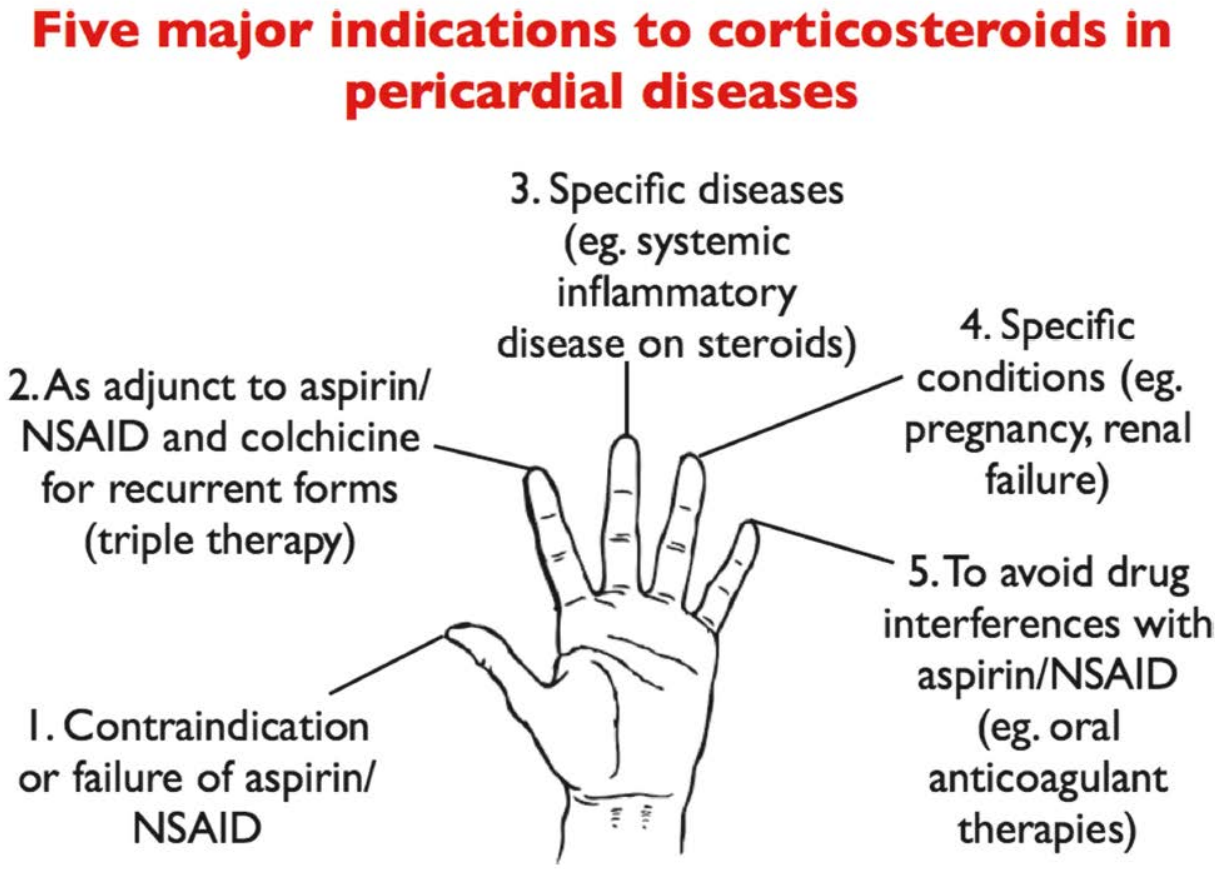
Registred indication in Italy from April 2017:
No more off-label

Side effects:
Diarrhoea about 8%
Elevation of transaminases 4%
Leucopenia, Alopecia<1%

Interactions:
Be aware if elderly and renal failure
Halved doses in the elderly and renal failure
Consider concomitant tx: statins, macrolids



Corticosteroids: 2° Level (LOE B)
Low to moderate doses
(e.g. prednisone 0.2-0.5 mg/kg/day) with slow tapering



Prednisone dose[a]	Starting dose 0.25–0.50 mg/kg/day[a]	Tapering[b]
Prednisone daily dose	>50 mg	10 mg/day every 1–2 weeks
	50–25 mg	5–10 mg/day every 1–2 weeks
	25–15 mg	2.5 mg/day every 2–4 weeks
	<15 mg	1.25–2.5 mg/day every 2–6 weeks

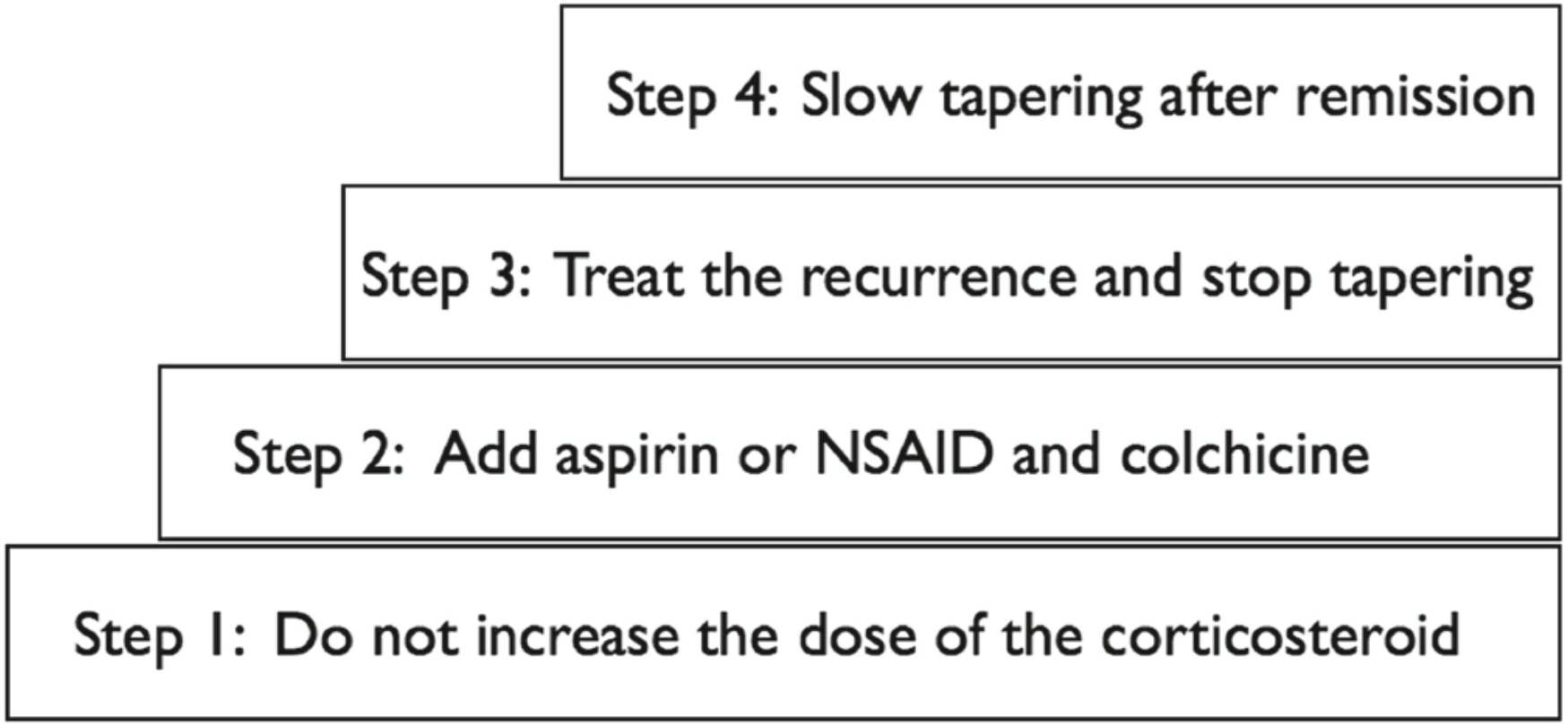
Calcium intake (supplement plus oral intake) 1,200–1,500 mg/day and vitamin D supplementation 800–1000 IU/day should be offered to all patients receiving glucocorticoids

[a]Avoid higher doses except for special cases and only for a few days, with rapid tapering to 25 mg/day. Prednisone 25 mg is equivalent to methylprednisolone 20 mg

[b]Every decrease in prednisone dose should be done only if the patient is asymptomatic and C-reactive protein is normal, particularly for doses <25 mg/day

Imazio M. Pericardial Diseases, Springer 2016

How to manage corticosteroid therapy in case of recurrences during tapering in 4 steps



Imazio M. Myopericardial Diseases, Springer 2016

Causes of Recurrent Pericarditis

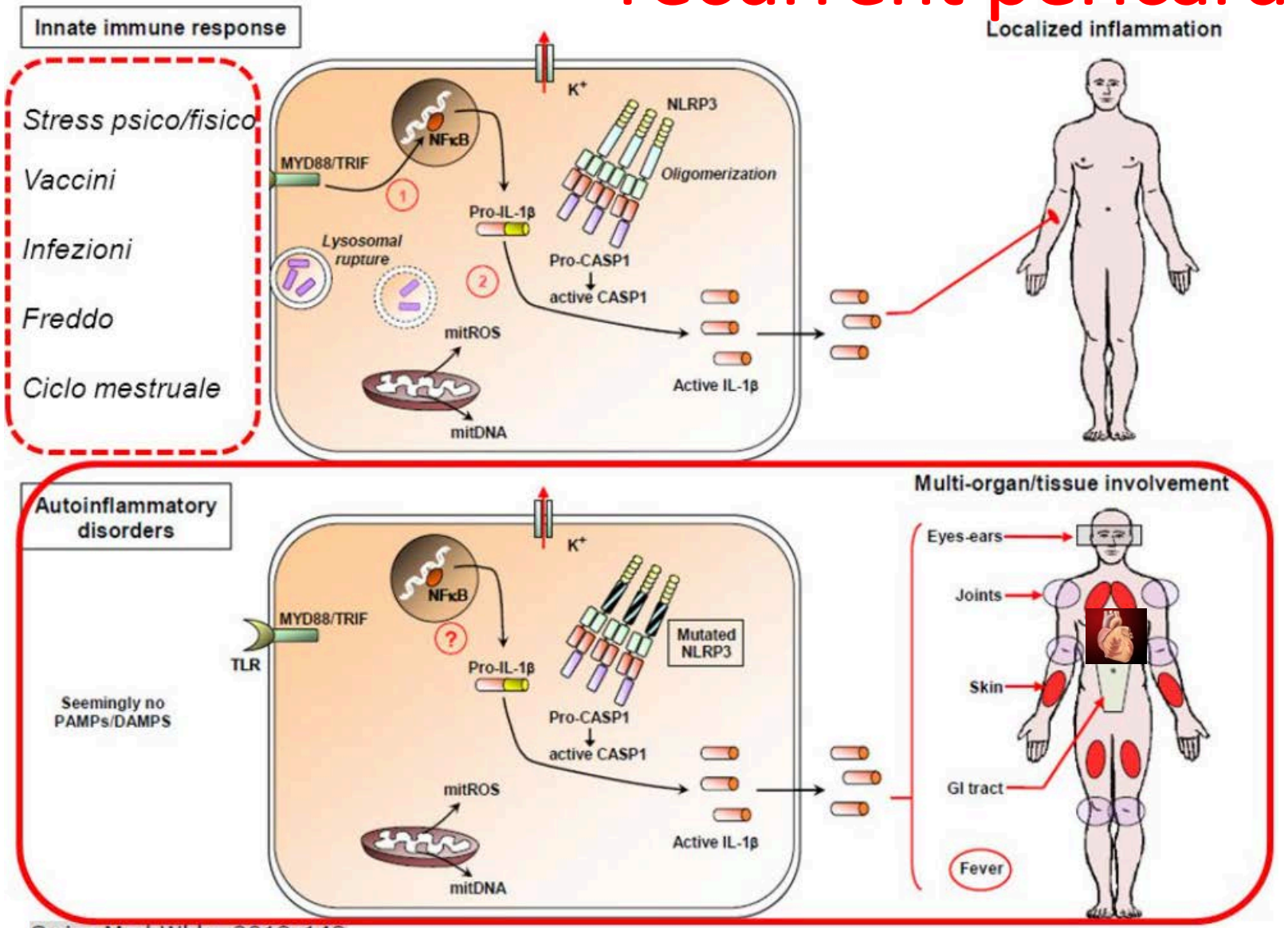
Cause	Frequency
Idiopathic	>60–70 %
Infectious (e.g. especially viral)	20–30 %
Systemic inflammatory diseases and pericardial injury syndromes	5–10 %
Autoinflammatory diseases	5–10 %[a]
Neoplastic pericardial diseases	5–10 %
Inadequate treatment of the first or subsequent attack of pericarditis	Unknown[b]

[a]Higher frequency should be suspected especially in children

[b]Inadequate treatment according to doses, duration and tapering and may include the lack of an adequate time of restriction of physical activities

Autoinflammatory diseases as a cause of recurrent pericarditis

7% TRAPS



Pericardium

Swiss Med Wkly. 2012;142

First level tx: Aspirin or NSAID plus colchicine

↓

Second level tx: Corticosteroids plus colchicine

↓

Third level tx: Aspirin/NSAID plus colchicine and Corticosteroids (Triple therapy)

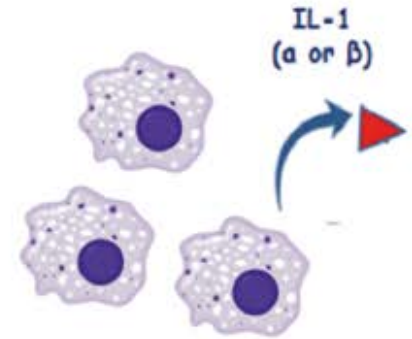
↓

Fourth level tx: Use of alternative drugs (e.g. azathioprine or IVIG or anakinra)

↓

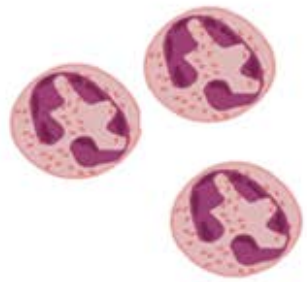
Fifth level tx: Pericardiectomy

Drug	Mechanism	Dosing	Duration	Monitoring	LOE
Aspirin	Anti-inflammatory (COX)	750-1000mg every 8h	1-2 weeks till remission then tapering	Blood count, renal function, CRP, Blood Pressure, Echo	A
NSAIDs	Anti-inflammatory (COX)	Ibuprofen: 600mg TID Indomethacin: 25-50mg TID	1-2 weeks till remission then tapering	Blood count, renal function, CRP, Blood Pressure, Echo	A

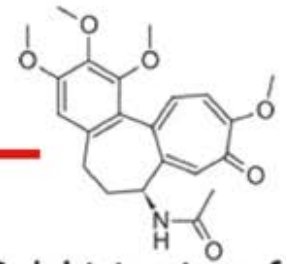


Activated monocytes and macrophages

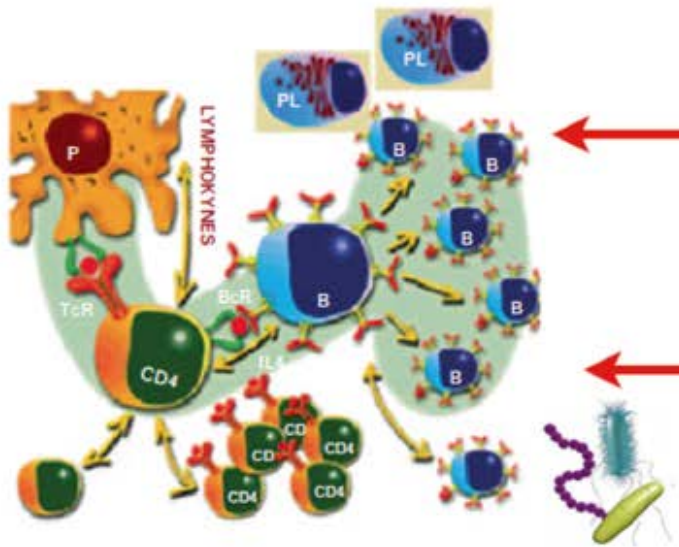
Anakinra competes with IL-1 and reduces IL-1 activity



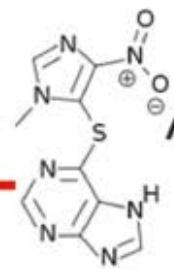
Granulocytes



Colchicine interferes with granulocytes function blocking tubulin polymerization



Immune response

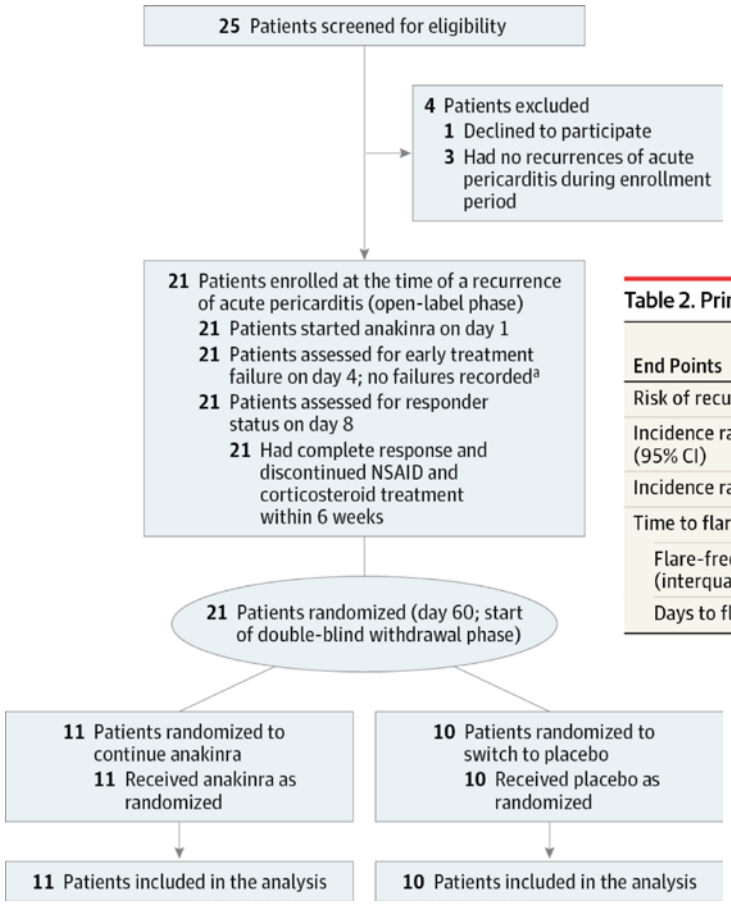


Azathioprine blocks purine and DNA synthesis and inhibits lymphocites proliferation

IVIGs modulate the the adaptative and innate immunity and increase the clearance of infectious agents

Infectious agents

Effect of Anakinra on Recurrent Pericarditis Among Patients With Colchicine Resistance and Corticosteroid Dependence The AIRTRIP Randomized Clinical Trial



Anakinra 100mg/day sc for 6 months

Table 2. Primary End Points: Pericarditis Recurrence Rate and Time to Flare After Randomization

End Points	Placebo (n=10)	Anakinra (n=11)	Difference (95% CI)	*P* Value
Risk of recurrence, No. (%)	9 (90)	2 (18)	−0.718 (−1.01 to −0.42)	.001[a]
Incidence rate, % patients/y (95% CI)	2.06 (1.07-3.97)	0.11 (0.03-0.45)	−1.95 (−3.3 to −0.6)	
Incidence rate ratio (95% CI)	1 [Reference]	0.055 (0.006-0.264)		<.001[b]
Time to flare				
Flare-free survival, median (interquartile range), d	72 (64-150)	Not calculable		<.001[c]
Days to flare, mean (range)[d]	28.4 (2-90)	76.5 (33-120)	−48.1 (−118.1 to 21.9)	<.001[e]

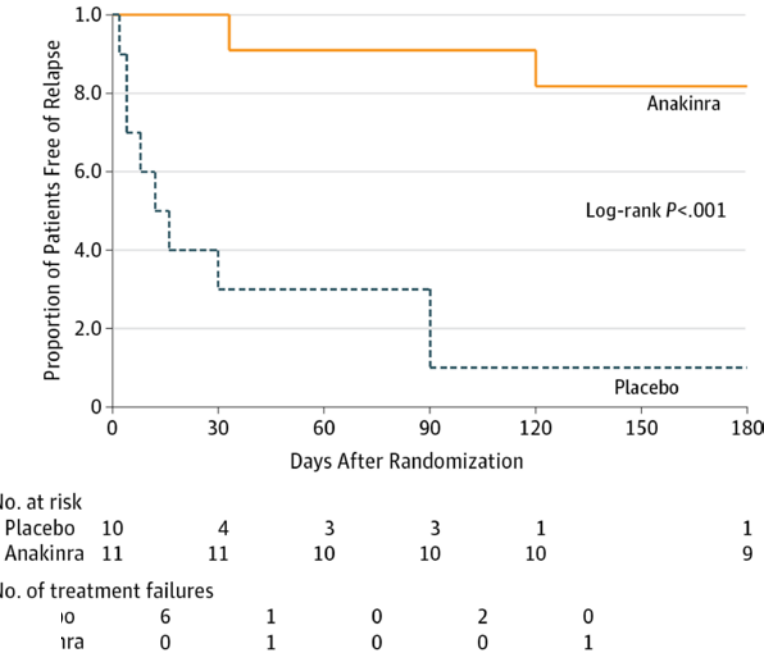


Table 3. Adverse Events in Anakinra-Treated Patients

Adverse Events	No. of Patients (%)		
	Open-Label Phase (n=21)	Double-Blind Withdrawal Phase (n=11)	Entire Study Period (n=21)
Overall adverse events	20 (95.2)	1 (9.1)	20 (95.2)
Infections[a]	1 (4.8)	0	1 (4.8)
Transaminase elevation	3 (14.3)	0	3 (14.3)
Local skin reactions	20 (95.2)	0	20 (95.2)
Ischemic optic neuropathy	0	1 (9.1)	1 (4.8)
Permanent drug discontinuation	0	0	0

[a] The infection adverse event was a case of herpes zoster.

JAMA. 2016;316(18):1906-1912

Complications and prognosis

- Recurrences in 20 to 30% of cases (pre-colchicine time) but halved by colchicine
- Risk of cardiac tamponade very low during follow-up if specific causes excluded (e.g. systemic inflammatory diseases, bacterial and neoplastic etiologies)
- Risk of constriction related to the etiology and not the number of recurrences (never reported in idiopathic recurrent pericarditis)

- 20-30% bacterial etiologies (TB, purulent)
- 2-5% neoplastic etiology, systemic inflammatory diseases, post-cardiac injury syndromes
- <1% viral or ”idiopathic” pericarditis

Circulation. 2011;124(11):1270-5

Conclusions

- Treatment of pericarditis should be targeted as much as possible to the underlying cause or mechanism (often not possible).
- Aspirin, NSAID plus colchicine are first line therapy.
- Corticosteroids (low-moderate doses with slow tapering) are a second line therapy with specific indications.
- In cases with failure of first and second line therapies (>2 recurrences) new emerging therapies include: anakinra (elevated CRP, periodic fever with possible autoinflammatory mechanism)> IVIGs > azathioprine.
- Pericardiectomy is a possible last option when all medical therapies fail.

Thank you very much for your attention!