

# Pain, Pericardial Effusion, Pericarditis What do I need to do?

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# **Objectives**

- Learn the diagnostic criteria of pericarditis
- Select the appropriate pharmacotherapy for acute and recurrent pericarditis
- Recognize indications for cardiology consultation in the management of pericarditis

### **Case - History**

 53 yo F with hypertension, chronic leukopenia with negative ANA, migraine headaches, hypothyroidism, and TIA x 2 provoked by oral contraceptive medications.



# **Case – History and Exam**

- Rheumatology consult 1 year ago to evaluate for possible Raynaud's → no vasculopathy
- Started hormonal replacement therapy for premature menopause at age 42
- Takes chlorthalidone for calciuria and hypertension

**Social History** 

• No tobacco, alcohol, or recreational drug use

Family History: Noncontributory

Physical exam

- Temp 97.8, HR 120 bpm, BP 156/89 mmHg, RR 12, O<sub>2</sub> Sat 100% RA
- Chest: CTA
- Cardiac: JVP 7 cm H<sub>2</sub>0, S1S2 irregularly irregular, no murmur or rub
- Abdomen: nondistended, nontender
- Ext: Trace bilateral edema

# **Question 1**

What is your differential of the patient's symptoms?

- A. Myocardial infarction
- B. Coronary artery vasospasm angina
- C. Costochondritis
- D. Esophagitis
- E. Pericarditis





### **Anatomy of the Pericardium**



Cremer PC et al. JAMA 2024;332:1090

### **Functions of the Pericardium**



# **Pathophysiology of Pericardial Inflammation**

#### POSSIBLE SIGNS OF ACUTE PERICARDITIS





Cremer PC et al. JAMA 2024;332:1090

### **Definition and Classification of Pericarditis**



# **Other Types of Pericarditis**

<b>Constrictive</b> Viral <1% Autoimmune 2-5% Bacterial 20-20%	<b>Effusive-</b> <b>Constrictive</b>				
Myopericarditis	Pericardial				
Elevated troponin	Tamponade <3%				

# **Question 2**

### What should you do next?

- A. No intervention and reassurance
- B. Start ibuprofen and follow-up in 2 weeks
- C. Start colchicine and follow-up in 2 weeks
- D. Obtain ECG
- E. Send patient to ED

# Diagnosis

#### Chest pain (85-90%)

Sharp

• Pleuritic

- Improve sitting up and leaning forward
- Per • Hig • Trip

### Pericardial friction rub (< 30%)

High-pitchTriphasic

• Left lower sternal border-apex





### ECG changes (25-60%)

• Wide-spread ST elevation

PR-segment depression



#### Pericardial effusion ( $\leq 60\%$ )

NewSmall

Klein AL et al. JACC: Cardiovasc Imag. 2024;17:937; JAMA Network. Three-component Pericardial Friction Rub

# **Diagnostic Tests**





- CBC
- CRP
  - ESR
  - Troponin
  - Thyroid levels

Adler Y et al. Eur Heart J. 2015;36:2921.

# Supportive Diagnostic Features – Acute and Recurrent Pericarditis

#### Patient presentation and history

- Low-grade fever
  Cough
- Fatigue
- Dyspnea

#### Laboratory evaluation

#### Elevated inflammatory marker levels

- Erythrocyte sedimentation rate
- C-reactive protein

#### Patients with low-grade fever and fatigue are more likely to have a high neutrophil count and/or an elevated neutrophil to lymphocyte ratio

#### Cardiac magnetic resonance (CMR) study

#### Abnormal CMR study finding of pericardial late gadolinium contrast enhancement (LGE)

LGE, or retention of gadolinium-based contrast, reflects degree of neovascularization and inflammation

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#### LGE must be interpreted with clinical setting due to variable presentations

Patients with LGE may have active pericarditis (see Figure 3)

Patients with thickened pericardium and no LGE have no active inflammation

#### Other important considerations

- Assess for elevated cardiac troponin levels, which can be indicative of myocardial ischemia or myocarditis
- Assess for suspected systemic autoimmune disease and family history of pericarditis at time of diagnosis
- Assess for tuberculosis for patients from or living in endemic areas

# **ECG – Widespread ST Elevation**

New and widespread ST-segment elevation with PR-segment depression (≈25%-50% of patients)



Pericarditis ECG changes can also be distinguished from J-point elevation by comparing with prior ECGs, if available Pericarditis may trigger atrial fibrillation or flutter ( $\approx 4\%$  of patients)

Crener PC et al. JAMA. 2024;332;1090

### **ECG – Pericarditis**



#### Nathanson LA, Goldberger AL. ECG Wave-Maven Case List

### **ECG – Pericarditis**



### **ECG – Inferior STEMI**



Chuan M, Goldberger AL. ECG Wave-Maven Case List

### **ECG – Cardiac Tamponade**



# **ECG – J Point ST Elevation**



Perry DL, Goldberg AL. ECG Wave-Maven Case List

### **Question 3**

ECG: Afib 128 bpm, no ST elevation or depression, normal voltage POCUS: large circumferential pericardial effusion

### What would you do next?

- A. Start metoprolol
- B. Start DOAC
- C. Start ibuprofen
- D. Start colchicine
- E. Send patient to ED

# **Etiologies**

#### Idiopathic

#### • 50-60%

Antecedent URI or gastroenteritis



#### Infectious

Viral (common) —

Coxsackie

SARS-CoV2

- → ~
- Herpes virus (EBV, CMV, adenovirus, Parvovirus B19)
- Bacterial
  - Tuberculosis —
  - Coxiella
- Fungal (very rare)
- Histoplasma
- Parasitic (very rare)
  - Echinococcus, Toxoplasma

#### Autoimmune (2.6%)

- Lupus (20%)
- Rheumatoid arthritis (asymptomatic pericardial effusion)
- Scleroderma
- Sjögren syndrome
- Systemic vasculitides
- Sarcoidosis
- Inflammatory bowel diseases

### Injury

- Myocardial infarction
- Open heart surgery
- Trauma
- Radio frequency ablation

#### Gourlet F et al. Am J Med. 2015;128:784 Cremer PC et al. JAMA 2024;332:1090

#### Metabolic (5%)

- Uremic
- Myxedema
- Hypoproteinemia
- Hypercalcemia
- Hyperparathyroidism

#### Malignancy (9%)

- Primary malignant
  - Lymphoma
  - Mesothelioma
  - Sarcoma
- Metastatic
  - Lung cancer (40%)
  - Breast (25%)
  - Hematologic (20%)

#### Medications

- Hydralazine
- Procainamide
- Methyldopa
- Penicillin
- Isoniazid
- Phenytoin
- Doxorubicin,
- cyclophosphamide

# Imaging

#### Echocardiography

(asterisk)

#### First-line and initial imaging test in suspected acute or recurrent pericarditis

- Characterization of pericardial effusion (location, size, rapidity of fluid accumulation)
- Hemodynamic consequences of effusion (pericardial tamponade, constrictive pathophysiology)
- Thickening of pericardium (hyperechoic)

Large effusion with cardiac tamponade

#### Cardiac magnetic resonance imaging (CMR)

#### Used with gadolinium-based contrast for recurrent pericarditis

- Characterization of severity of pericardial inflammation
- Late gadolinium contrast enhancement (LGE) correlating to extent of neovascularization

Substantial LGE indicative of vascularization and current or prior inflammation (blue arrowhead)

Increased T2-STIR signal intensity indicative of

edema and active inflammation (blue arrowhead)

#### Cardiac computed tomography (CT)

#### May be used for procedural and surgical planning in acute or recurrent pericarditis

- Evidence of pericardial pathology when CT is obtained for alternate reason
- Can be used in procedural planning prior to pericardiocentesis, pericardial window, or pericardiectomy



CT indicating extent of pericardial calcification prior to pericardiectomy (blue arrowhead)



Clinical examples

Assessment capabilities



Cremer PC et al. JAMA 2024;332:1090



# **Diagnostic and Therapeutic Algorithm**



Klein AL et al. JACC: Cardiovasc Imag. 2024;17:937

# **Diagnostic and Therapeutic Algorithm**



Klein AL et al. JACC: Cardiovasc Imag. 2024;17:937

# **Anti-Inflammatory Treatments**

Drug and dose	Duration	Tapering	Common adverse effects <sup>a</sup>
Acute or recurrent pericarditis			
Aspirin (500-1000 mg 3 times daily)	Until chest pain has resolved and CRP normalized (typically 1-2 wk for the initial episode) Weeks to months for recurrence	250- to 500-mg Decrease every 1-2 wk	Gastrointestinal (dyspepsia, peptic ulcer disease) Kidney (acute kidney injury) Cardiovascular (fluid retention, worsening of underlying hypertension)
Colchicine (0.5 to 1.2 mg daily) (<70 kg: 0.5 or 0.6 mg daily; >70 kg: 0.5 or 0.6 mg twice daily)	Acute: 3 mo Recurrence: ≥6 mo	Optional (eg, can decrease to once daily or every other day prior to discontinuation)	Gastrointestinal (diarrhea [23%], nausea, vomiting)
lbuprofen (600-800 mg 3 times daily)	Until chest pain has resolved and CRP normalized (typically 1-2 wk for the initial episode) Weeks to months for recurrence	200- to 400-mg Decrease every 1-2 wk	Gastrointestinal (dyspepsia, peptic ulcer disease) Kidney (acute kidney injury, worsening of underlying hypertension)
Prednisone (0.25-0.5 mg/kg/d)	Weeks to months	Rapid dosage tapering to 25 mg/d Starting dose 15-25 mg: decrease 2.5 mg/d every 2-4 wk Starting dose <15 mg: decrease 1.25-2.5 mg/d every 2-6 wk Can taper more quickly (eg, 8 wk) in patients taking an IL-1 blocker	Cardiovascular (hypertension, fluid retention) Psychiatric (depression, agitation) Endocrine (cushingoid appearance, hyperglycemia, osteoporosis) Gastrointestinal (peptic ulcer, ulcerative esophagitis) Infections Myopathy Glaucoma

# **Colchicine Trials**

	ICAP (n = $240$ ) <sup>37</sup>	COPPS-2 (n = 360) <sup>14</sup>	$CORP (n = 120)^3$	$CORP-2 (n = 240)^4$
Cause of pericarditis, %	Idiopathic: 77.1 PCIS: 20.0 Connective tissue disease: 2.9	Not applicable	Idiopathic: 81.7 PCIS: 5.8 Connective tissue disease: 12.5	Idiopathic: 82.5 PCIS: 8.8 Connective tissue disease: 6.7
Pericarditis episodes	Acute	Prevention of PCIS	First recurrence	Multiple recurrences
Co-interventions, %	Aspirin or ibuprofen: 93.3 Prednisone: 6.7	None	Aspirin or ibuprofen: 92.5 Prednisone: 7.5	Aspirin or indomethacin: 93.3 Prednisone: 6.7
Primary end point	Incessant or recurrent pericarditis	PCIS	Recurrent pericarditis	Recurrent pericarditis
Follow-up, mo	18	18	18	18
Event rates (absolute risk reduction), %	37.5 vs 16.7 (absolute risk reduction, 20.8)	29.4 vs 19.4 (absolute risk reduction, 10.0)	55 vs 24 (absolute risk reduction, 31)	42.5 vs 21.6 (absolute risk reduction, 20.9)

Colchicine has not been studied in tuberculous or autoimmune pericarditis.

Cremer PC et al. JAMA 2024;332:1090;<sup>37</sup>Rodriguez de la Serna et al. Lancet 1987;2:1517; <sup>14</sup>Isiguzo G et al. Curr Cardiol Rep 2020;22:2; <sup>4</sup>Imazio M et al. Lancet 2014;383:2232.

# **Anti-inflammatory Medications - Steroids**

Starting dose 0.25–0.50 mg/kg/day <sup>a</sup>	Tapering <sup>b</sup>
>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

- Triple therapy add corticosteroids to ASA/NSAIDS and colchicine, not replacement
- Taper when asymptomatic or CRP is normal
- Calcium 1,200-1,500 mg/day
- Vitamin D 800-1,000 IU/day
- Bisphosphonates in men ≥ 50 years and post-menopausal women at initial prednisone dose ≥5-7.5 mg/day

# **IL-1 Blockers Trials**

#### Table 2. Randomized Withdrawal Trials With IL-1 Blockers in Recurrent Pericarditis

	Anakinra (n = 21) <sup>22</sup> AIRTRIP	Rilonacept (n = 61) <sup>23</sup> RHAPSOD	Goflikicept (n = 20) <sup>42</sup>
Cause of recurrent pericarditis	Idiopathic	Idiopathic: 85% PCIS: 15%	Idiopathic
No. of prior recurrences for enrollment	At least 3 prior recurrences (mean, 6.8)	At least 2 prior recurrences (mean, 4.7)	At least 1 prior recurrence (45%, ≥3 recurrences)
Disease state at enrollment	Active (elevated CRP) >10 mg/dL	Active (elevated CRP)	Active: 41% Quiescent: 59%
Background therapy, %	Corticosteroids: 100 NSAIDs: 71.4 Colchicine: 85.7	Corticosteroids: 45.9 NSAIDs: 63.9 Colchicine: 86.9	Corticosteroids: 9.1 <sup>a</sup> NSAIDs and/or colchicine: 90.9 <sup>a</sup>
Tapering during run-in phase	NSAIDs stopped within 15 d; corticosteroids stopped by wk 7; colchicine discontinuation optional (57% continued)	Prespecified discontinuation of NSAIDs, colchicine, and corticosteroids by wk 10; median time to monotherapy 7-8 wk	NSAIDs and colchicine stopped on day 14 without tapering; corticosteroids stopped by wk 12
Primary end point	Recurrence (pericardial chest pain with CRP elevation)	Recurrence (pericardial chest pain with CRP elevation)	Recurrence (2 of the following: pericardial chest pain, CRP elevation, new or worsening pericardial effusion)
Randomized withdrawal follow-up	6 mo	Event driven; median time to recurrence with placebo was 8.6 wk	24 wk
Event rates, %	90.0 vs 18.2	74.2 vs 6.7	90.0 vs 0

Abbreviations: CRP, C-reactive protein; NSAID, nonsteroidal anti-inflammatory drug; PCIS, post-cardiac injury syndrome.

<sup>a</sup> For run-in period (n = 22).

Cremer PC et al. JAMA 2024;332:1090; <sup>22</sup>Brucato A et al. JAMA 2016;316:1906;<sup>23</sup>Klein AL et al. NEJM 2021;384:31; <sup>42</sup>Myachikova VY et al. JACC 2023;82:30

# **Anti-Inflammatory Treatments**

Recurrent pericarditis	At least 6-12 mo, with longer	Optional (decrease by 100 mg per wk	Infection (39%; serious infection, 2%-3%; mos
Anakinra (1-2 mg/kg/d, with a maximum dose of 100 mg subcutaneously daily)	durations in multiple recurrent pericarditis	every month after several months of stability with daily therapy or decrease to every other day for 3 mo followed by half dose every other day for an additional 3 mo) <sup>b</sup>	commonly upper respiratory tract infections) Injection site reactions (71%)
Rilonacept (320 mg subcutaneously as a loading dose, followed by 160 mg weekly as a maintenance dose)	At least 6-12 mo, with longer durations in multiple recurrent pericarditis	Not investigated	Infection (34%-48%, most commonly upper respiratory tract infections) Injection site reactions (48%)

# **Treatment Approach**

#### Patient presents with acute pericarditis

#### Initial occurrence of acute pericarditis

- High-dose nonsteroidal anti-inflammatory drugs (NSAIDs) until chest pain resolves and C-reactive protein (CRP) level is normal
- ► Colchicine for 3 mo

#### First recurrence

- NSAIDs until chest pain resolves and inflammatory markers are normal
- ► Colchicine for ≥6 mo

#### Second recurrence

- Addition of IL-1 blocker for idiopathic pericarditis or post-cardiac injury syndrome if colchicine-resistant and a history of prior C-reactive protein elevation
- Low to moderate dose of prednisone (0.25-0.5 mg/kg daily) for patients with underlying systemic autoimmune disease

# **Myopericarditis**

### Diagnosis

- Pericarditis
- Positive troponin or CK-MB
- CMR
- No regional or global LV systolic dysfunction on echo or CMR

### **First-line Therapy**

- Aspirin: 1,500-3,000 mg/d
- Ibuprofen: 1,200-2,4000 mg/d
- Indomethacin: 75-150 mg/d

### Second-line Therapy

Corticosteroids

### Exercise

- Avoid exercise beyond sedentary activities
- Resume exercise after 6 months

# Myocarditis with pericardial involvement

 Presence of regional or global LV systolic dysfunction

### Etiology

- Cardiotropic virus
  - Coxsackie
- Cardiotoxic agents
  - Chemotherapy
  - Immune checkpoint inhibitors
  - Methamphetamine
  - Cocaine
- Systemic immune diseases
  - Lupus
  - Rheumatoid arthritis
  - Sarcoidosis
  - Hypereosinophilia

# **Pericardial Effusion**

### Onset

- Acute
- Subacute
- Chronic (>3 months)

#### Size

- Small (<10 mm)
- Moderate (10-20 mm)
- Large (>20 mm)

#### Distribution

- Circumferential
- Loculated

#### Etiology

- Idiopathic (up to 50%)
- Malignancy (10-25%)
- Infection (15-30%)
- Connective tissue disease (5-15%)
- latrogenic (15-20%)
- TB (>60%) *developing countries*

### Presentation

- Asymptomatic/incidental finding on echo/CT/CMR
- CXR enlarged cardiac silhouette
- Dyspnea, nausea, cough, hoarseness, dysphagia

#### Management

- Assess for tamponade
- If inflammatory signs, treat with antiinflammatory medications
- Moderate and large refer to cardiology
- Large effusion → pericardiocentesis
- Re-accumulation → pericardial window

#### Prognosis

- Moderate and large: 30-35% develop tamponade
- Mild no surveillance echo unless symptoms
- Moderate echo every 6 months
- Large echo every 3-6 months

Adler Y et al. Eur Heart J. 2015;36:2921. Created in Biorender.com

### **Pericardial Effusion Size**



# **Constrictive Pericarditis**

#### **Risk of Progression**

- Viral and idiopathic (<1%)
- Immune-mediated, neoplastic (2-5%)
- Bacterial, purulent (20-30%)

#### Prevalence

- Idiopathic or viral (42-49%)
- Post-cardiac surgery (11-37%)
- Post radiation therapy: Hodgkin's lymphoma and breast (9-31%)
- TB, purulent (3-6%) developed countries
- Other (<10%)

#### Subtypes

- Transient
- Effusive-constrictive
  - RAP >10 mmHg or not decreased by 50% after pericardiocentesis
- Chronic: (Symptoms >3-6 months)
- End-stage chronic
  - CI <1.2 L/mm<sup>2</sup>
  - Cirrhosis
  - Hypoalbuminemia from proteinlosing enteropathy

Adler Y et al. Eur Heart J. 2015;36:2921. Created in Biorender.com

#### Presentation

- Fatigue
- Peripheral edema
- Abdominal swelling
- Right heart failure symptoms with preserved right and left systolic function

#### Diagnosis

- Elevated LFTs, pro-BNP
- ECG
  - nonspecific ST change
  - atrial fibrillation
- CXR: 33% pericardial calcification
- Echo
  - septal bounce
  - medial e' >8 cm/s
  - hepatic vein end-diastolic expiratory reversal velocity/forward flow ratio: >0.8, annulus reversus
- CT
  - increased pericardial thickening
  - pericardial calcification
- CMR
  - increased pericardial thickening
  - septal shift
  - late gadolinium pericardial enhancement (LGE)
  - pericardial edema and inflammation (T2-STIR)
- Cardiac Cath
  - square root sign
  - RVEDP=LVEDP, ventricular interdependence

#### Management

- Transient
  - Anti-inflammatory therapy
- Effusive-constrictive
  - Pericardiocentesis →anti-
  - inflammatory medications →
  - visceral pericardiectomy
  - (perioperative mortality 6-12%)
- Chronic
  - Visceral pericardiectomy

### **Spectrum of Pericardial Diseases and CMR Findings**



### **Uremic, Inflammatory, and Post Cardiac Injury Pericarditis**



• May need to avoid anticoagulants

Adler Y et al. Eur Heart J. 2015;36:2921. Created in Biorender.com

- No therapy if post-operative asymptomatic pericardial effusion
- Anti-inflammatory medications if symptomatic
- Post Afib ablation
  - Colchicine prophylaxis post Afib ablation (OR 0.38)

### **Neoplastic Pericarditis**



#### Presentation

- Any size
- Frequently tamponade

#### Management

- Drainage
- Pericardial window
- Intrapericardial cytostatic/sclerosing agents (cisplatin/tetracycline)
- Radiation therapy
  - Lymphoma
  - Leukemias
- Pleuropericardiotomy

Adler Y et al. Eur Heart J. 2015;36:2921. Created in Biorender.com

# **Question 4**

When would it be appropriate to refer your patient to cardiology?

- A. Lack of response to anti-inflammation medications
- B. Third recurrent episode, incessant, or chronic pericarditis
- C. Large pericardial effusion
- D. Constrictive pericarditis
- E. All of the above

# **Knowledge Gaps**

- Optimal treatment for
  - incessant pericarditis
  - severe first recurrence
  - Effuse constrictive pericarditis
  - Tuberculous pericarditis
- Efficacy of therapies in autoimmune disease
- Optimal treatment duration for multiple recurrent pericarditis
- Optimal tapering doses and duration of treatment
- Role of radical pericardiectomy in multiple recurrent
  pericarditis without constrictive physiology

# **Case – 1<sup>st</sup> Hospitalization**

 53 yo F with hypertension, chronic leukopenia with negative ANA, migraine headaches, hypothyroidism, and TIA x 2 provoked by oral contraceptive medications.



# **Case – Treatment and Labs**

	Treatment	WBC	HB	НСТ	PLT	ESR	CRP	Pro-BNP	GFR
1/26/22		3.14	13.2	38.9	309	7	0.2		106
8/24/23		2.19	12.3	35.4	257				
4/4/24 Hosp #1	Ibuprofen x 2 weeks Colchicine	8.2	12.2	35.6	336		85.6	942	112
4/15/24		10.13	12.5	37.1	507	51			
4/22/24							70.7		112
4/25/24 Hosp #2	Colchicine	8.01	10.6	31.8	504	56			
5/3/24	d/c colchicine Start anakinra	3.59	9.6	29	480	53	53		
5/8/24							39.8		
6/26/24		3.03	11.6	36.1	269	14	0.3		
9/17/24		2.58	11.9	34.6	249	2			112
12/15/24	Taper anakinra								

# **Key Points**

- Echocardiography is the first line imaging modality in the evaluation of pericardial effusion and pericarditis
- Cardiac MRI and CT are second-line imaging modalities that can access pericardial calcification, characterization of effusion, and tissue inflammation
- NSAIDs and colchicine are the first-line pharmacotherapy for management acute pericarditis
- Corticosteroid and anti-IL-1 inhibitors are second and third-line pharmacotherapies for management of chronic or recurrent pericarditis
- Corticosteroid and IL-1 blockers discontinuation is associated with a high incident of recurrent pericarditis
- Radical surgical pericardiectomy for patients with chronic constrictive pericarditis