CARDIAC SARCOIDOSIS: DIAGNOSTIC CHALLENGES & THERAPEUTIC INNOVATION

David Mintz, DO

Advanced Heart Failure and Transplant Cardiology

Northshore University Hospital

DISCLOSURES:

None

SARCOIDOSIS

- Multisystem granulomatous disease of unknown etiology; hallmark is formation of non-caseating granulomas

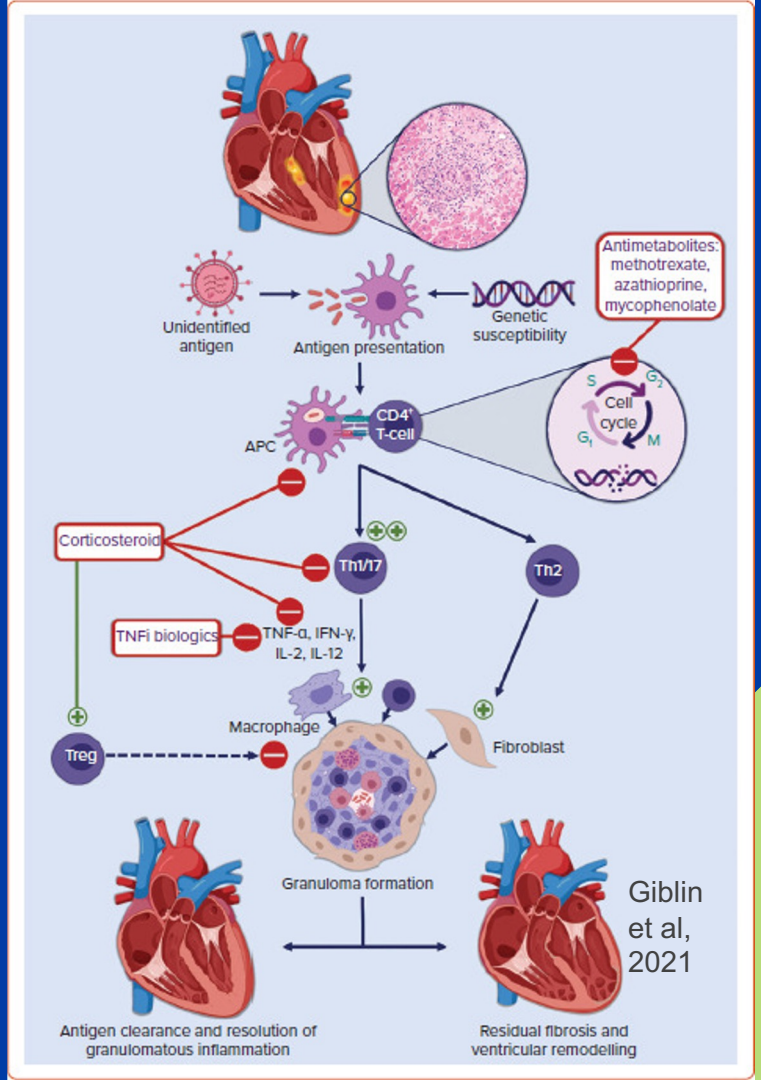
- The annual incidence of sarcoidosis in the United States is estimated at 35.2/100,000.
  - Higher among African Americans and Scandinavians
  - Women > Men
  - Commonly diagnosed 30-50 y/o

- Commonly causes HF as well as a variety of arrhythmias

- Estimated 20-25% of patients with pulmonary sarcoidosis have Cardiac Sarcoidosis (CS)

PATHOPHYSIOLOGY

- Dysregulation of immune response including activation of T-helper cells and upregulation of cytokines and chemokines, including INF-γ, TNF-α, TNF-β, IL-2, IL-12, and others.
- Likely genetic predisposition
- Potentially related to environmental exposure
  - I.e. (including mold, insecticides, or silica dust)
- Active Inflammatory Phase and Fibrotic Phase



Giblin et al, 2021

Phase	Pathology	Reversibility
Inflammation	Edema, active granulomas	✅ Potentially reversible
Granulomatous Inflammation	Mature granulomas replacing myocardium	⚠️ Partially reversible
Fibrosis	Dense scar replacing granulomas	❌ Irreversible

Preferred locations:

- Basal interventricular septum → conduction disease
- LV free wall (lateral, inferior)
- Papillary muscles → mitral regurgitation
- RV involvement increasingly recognized
- Distribution is **patchy and multifocal**

FOUR MAJOR PRESENTATIONS

- **Conduction Disease (25–30%)**
  - High-grade AV block — often the earliest sign
  - Bundle branch blocks
  - ⚡ AV block in patient **< 60 years** → think sarcoidosis

- **Ventricular Arrhythmias (25–30%)**
  - Monomorphic VT, polymorphic VT, VF
  - Can occur with **preserved LVEF**
  - VT storm may be the presenting feature

- **Heart Failure (25–30%)**
  - Mimics DCM or ischemic cardiomyopathy
  - Regional WMAs in **non-coronary distribution**

- **Sudden Cardiac Death (5–15%)**
  - May be the **first manifestation**

CLINICAL RED FLAGS: WHEN TO THINK CARDIAC SARCOIDOSIS

- Unexplained AV block in patient **< 60 years old**
- New cardiomyopathy with **non-coronary regional WMAs**
- Sustained VT with **preserved or mildly reduced EF**
- Known extracardiac sarcoidosis + **any cardiac symptom or ECG abnormality**
- Cardiomyopathy + **bilateral hilar lymphadenopathy** on CXR/CT
- **Basal septal thinning** on echo or CMR
- Young patient with HF and **multifocal mid-myocardial LGE** on CMR
- Unexplained syncope in a young/middle-aged patient
- Apparent Arrhythmogenic cardiomyopathy— consider sarcoidosis in the differential

ECG & ECHO

- Both have limited sensitivity and specificity

- ECG
  - Conduction delay
  - AVB
  - BBB: Right or Left

- Echo
  - Reduced EF
  - Regional wall aneurysm
  - Basal Septal thinning

CMRI W/ GADOLINIUM

- 95% Sensitive 85% Specific

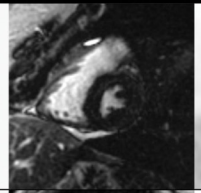
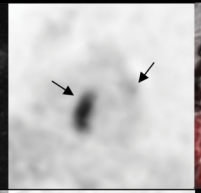
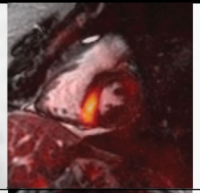
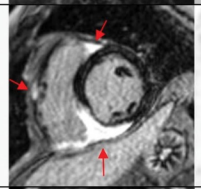
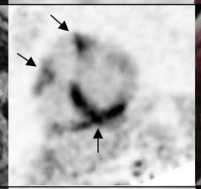
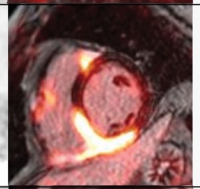
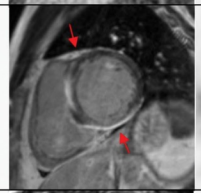
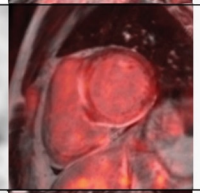
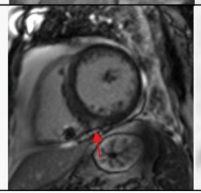
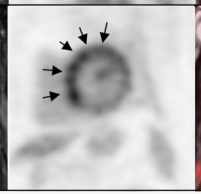
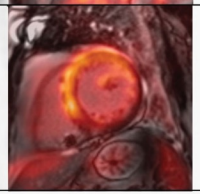
- LGE : Washes out slowly from areas of fibrosis or inflammation
  - Either inflammation or scar/fibrosis related to sarcoid
  - Patchy pattern

FDG PET

- FDG:
  - Glucose analogue, accumulates in areas of high metabolism
  - 24 hr ketogenic diet required for myocardial FDG suppression

- Assess activity

- Hallmark: Patchy uptake with perfusion mismatch
  - Occasionally with perfusion defect w/o uptake

Phenotypes	CMR	FDG PET	PET-MR	Typical Presentation
A Focal septal FDG uptake with or without corresponding LGE				Heart block
B Multifocal LGE and FDG uptake in a pattern consistent with cardiac sarcoidosis				Heart block Ventricular arrhythmias LV systolic dysfunction
C Multifocal LGE in a pattern consistent with cardiac sarcoidosis without FDG uptake				Ventricular arrhythmias LV systolic dysfunction
D LGE or FDG uptake in a pattern NOT consistent with cardiac sarcoidosis				Miscellaneous, including other presentations, such as palpitations, dyspnea, dizziness, ventricular ectopy

PATHOLOGIC DIAGNOSIS

- EMB:
  - Unguided yield ~20%
  - Increases with guidance (i.e. voltage map guided); ~40-50%
- LV Apical Core
- Explant Pathology
- Extracardiac Biopsy
  - Most commonly LN

DIAGNOSTIC CRITERIA

HRS criteria	2014	Definite CS: histological diagnosis from myocardial tissue CS is diagnosed in the presence of noncaseating granuloma on histological examination of myocardial tissue with no alternative cause identified Probable CS: clinical diagnosis from invasive and noninvasive studies There is a histological diagnosis of extracardiac sarcoidosis, and 1 of the following is present: Immunosuppressant-responsive cardiomyopathy or heart block Unexplained reduced LVEF <40% Unexplained sustained VT or high-degree AVB Patchy FDG uptake on a dedicated cardiac PET in a pattern consistent with CS LGE on CMR in a pattern consistent with CS Positive ^{67}Ga uptake in a pattern consistent with CS And other causes have been reasonably excluded.
WASOG criteria	2014	Granulomatous inflammation has been demonstrated in another organ and 1 of the following: Treatment-responsive cardiomyopathy and AVB Reduced LVEF in the absence of other risk factors Spontaneous or inducible sustained VT with no risk factors High-degree AVB Patchy uptake on a dedicated cardiac PET LGE on CMR Positive ^{67}Ga uptake Defect on perfusion scintigraphy or SPECT scan T2 prolongation on CMR And alternative causes have been reasonably excluded

JCS criteria (with systemic involvement)	2016	Histologic diagnosis group EMB or surgical specimens demonstrate noncaseating granulomas Clinical diagnosis group Those with negative myocardial biopsy or not undergoing myocardial biopsy. The patient is clinically diagnosed as having CS when: 2 or more of the 5 major criteria are satisfied OR 1 in 5 major and ≥2 minor criteria are satisfied: Major criteria: High-degree AVB or fatal VT/VF Basal thinning of the ventricular septum or abnormal ventricular wall anatomy LV contractile dysfunction ^{67}Ga or FDG-PET reveals abnormally high tracer uptake in the heart CMR reveals LGE of the myocardium Minor criteria: Abnormal ECG findings (nonsustained VT, premature ventricular complexes, bundle-branch block, axis deviation, abnormal Q waves) Perfusion defects on SPECT Monocyte infiltration and moderate fibrosis on EMB AND Granulomas are found in organs other than the heart OR the individuals show clinical findings strongly suggestive of pulmonary or ophthalmic sarcoidosis AND at least 2 of 5 characteristic findings of sarcoidosis are present: Bilateral hilar lymphadenopathy Elevated angiotensin-converting enzyme or serum lysozyme levels Elevated serum soluble interleukin-2 receptor levels Significant tracer accumulation in ^{67}Ga citrate scintigraphy or FDG-PET A high percentage of lymphocytes in bronchoalveolar lavage fluid with a CD4/CD8 ratio>3.5
JCS criteria (isolated cardiac sarcoidosis)	2016	Histological diagnosis group EMB or surgical specimens demonstrate noncaseating granulomas Clinical diagnosis group Those with negative myocardial biopsy or not undergoing myocardial biopsy; isolated CS is diagnosed clinically when there is significant tracer accumulation in ^{67}Ga citrate scintigraphy or FDG-PET and at least 3 of the other major criteria are satisfied: Major criteria: High-degree AVB or fatal VT/VF Basal thinning of the ventricular septum or abnormal ventricular wall anatomy LV contractile dysfunction CMR reveals LGE of the myocardium AND the following prerequisites are met: No clinical findings of sarcoidosis in any organs other than the heart ^{67}Ga citrate scintigraphy or FDG-PET reveals no abnormal tracer uptake in organs other than the heart Chest CT shows no findings consistent with pulmonary sarcoidosis (shadow along lymphatic tracts in the lungs or hilar/mediastinal lymphadenopathy >10 mm) Coronary artery disease and other inflammatory myocardial diseases are ruled out

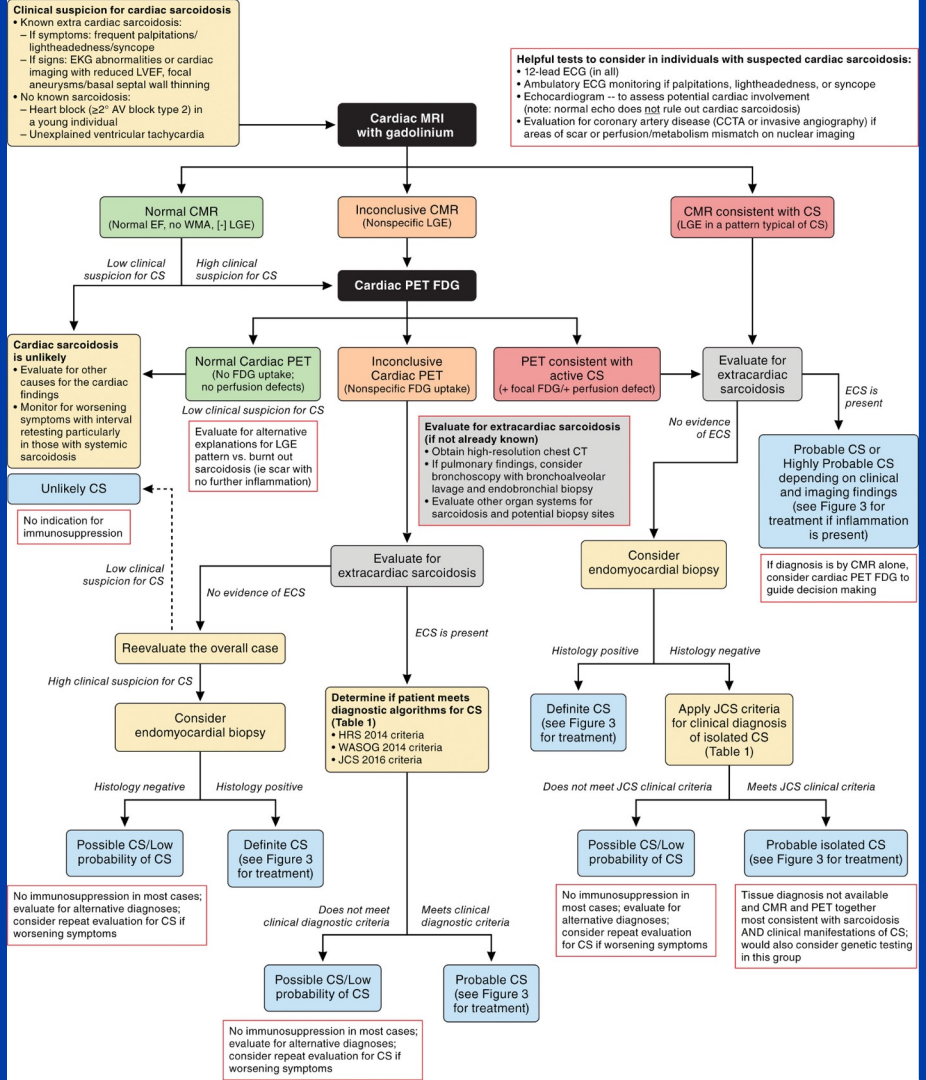
PROPOSED CRITERIA

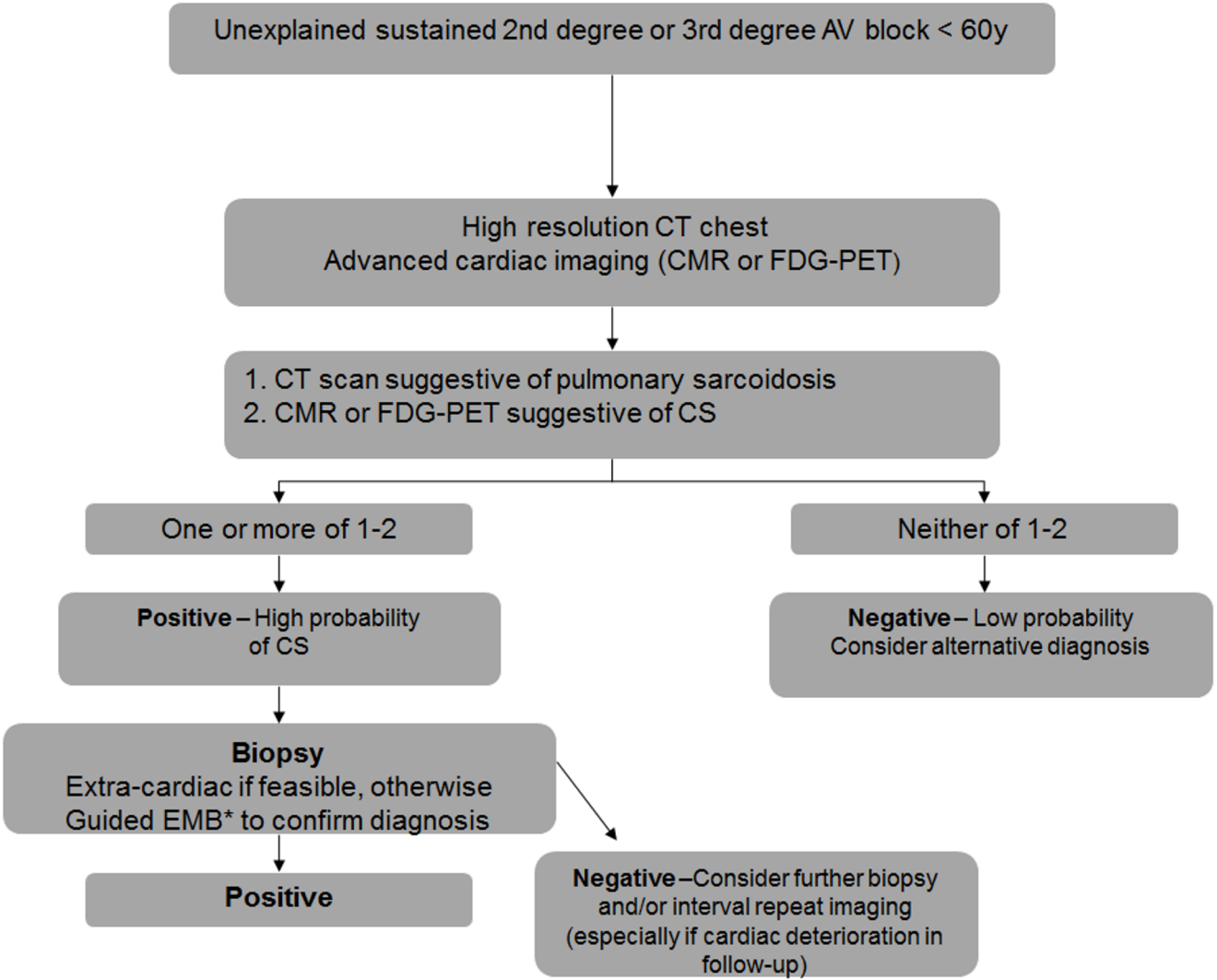
Diagnostic category of cardiac sarcoidosis	Criteria
Definite CS	Detection of a noncaseating granuloma on histological examination of myocardial tissue (EMB or other myocardial specimens) with no alternative cause identified
Uncertain diagnosis	
Highly probable CS	Requires all 4 of the following criteria: Confirmed diagnosis of extracardiac sarcoidosis Clinical findings consistent with CS* Imaging finding by CMR or FDG-PET consistent with CS Other potential causes for the clinical and imaging findings have been excluded
Probable CS	With histological diagnosis of extracardiac sarcoidosis; requires both of the following criteria: One of the following types of cardiac findings: Clinical findings consistent with CS* Imaging finding by CMR or FDG-PET consistent with CS Other potential causes for the clinical and imaging findings have been excluded
	Without histological or clinical diagnosis of extracardiac sarcoidosis; requires all 3 of the following criteria: Imaging findings by both CMR and FDG-PET consistent with CS 1 or more clinical findings consistent with CS* Other potential causes for the clinical and imaging findings have been excluded
Possible or low probability of CS	Includes patients with or without a histological or clinical diagnosis of extracardiac sarcoidosis not meeting criteria for definite, highly probable, or probable CS

CMR indicates cardiac magnetic resonance; CS, cardiac sarcoidosis; EMB, endomyocardial biopsy; FDG, fluorodeoxyglucose; and PET, positron emission tomography.

* Clinical findings consistent with CS may include unexplained left or right ventricular dysfunction, ventricular arrhythmias, or high-grade heart block.

Modified from Ozutemiz et al,[40] Orii et al,[42] Crouser et al,[57] and Yafasova et al.[58]


Clinical suspicion for cardiac sarcoidosis
• Known extra cardiac sarcoidosis:
– If symptoms: frequent palpitations/ lightheadedness/syncope
– If signs: EKG abnormalities or cardiac imaging with reduced LVEF, focal aneurysms/basal septal wall thinning
• No known sarcoidosis:
– Heart block (≥2° AV block type 2) in a young individual
– Unexplained ventricular tachycardia
Cardiac MRI with gadolinium
Helpful tests to consider in individuals with suspected cardiac sarcoidosis:
• 12-lead ECG (in all)
• Ambulatory ECG monitoring if palpitations, lightheadedness, or syncope
• Echocardiogram -- to assess potential cardiac involvement (note: normal echo does not rule out cardiac sarcoidosis)
• Evaluation for coronary artery disease (CCTA or invasive angiography) if areas of scar or perfusion/metabolism mismatch on nuclear imaging
Normal CMR (Normal EF, no WMA, [-] LGE)
Inconclusive CMR (Nonspecific LGE)
CMR consistent with CS (LGE in a pattern typical of CS)
Low clinical suspicion for CS
High clinical suspicion for CS
Cardiac PET FDG
Cardiac sarcoidosis is unlikely
• Evaluate for other causes for the cardiac findings
• Monitor for worsening symptoms with interval retesting particularly in those with systemic sarcoidosis
Normal Cardiac PET (No FDG uptake; no perfusion defects)
Inconclusive Cardiac PET (Nonspecific FDG uptake)
PET consistent with active CS (+ focal FDG/+ perfusion defect)
Evaluate for extracardiac sarcoidosis
ECS is present
Low clinical suspicion for CS
Evaluate for alternative explanations for LGE pattern vs. burnt out sarcoidosis (ie scar with no further inflammation)
Evaluate for extracardiac sarcoidosis (if not already known)
• Obtain high-resolution chest CT
• If pulmonary findings, consider bronchoscopy with bronchoalveolar lavage and endobronchial biopsy
• Evaluate other organ systems for sarcoidosis and potential biopsy sites
No evidence of ECS
Probable CS or Highly Probable CS depending on clinical and imaging findings (see Figure 3 for treatment if inflammation is present)
If diagnosis is by CMR alone, consider cardiac PET FDG to guide decision making
Unlikely CS
No indication for immunosuppression
Low clinical suspicion for CS
Evaluate for extracardiac sarcoidosis
No evidence of ECS
Consider endomyocardial biopsy
Reevaluate the overall case
High clinical suspicion for CS
ECS is present
Histology positive
Histology negative
Consider endomyocardial biopsy
Determine if patient meets diagnostic algorithms for CS (Table 1)
• HRS 2014 criteria
• WASOG 2014 criteria
• JCS 2016 criteria
Definite CS (see Figure 3 for treatment)
Apply JCS criteria for clinical diagnosis of isolated CS (Table 1)
Histology negative
Histology positive
Does not meet JCS clinical criteria
Meets JCS clinical criteria
Possible CS/Low probability of CS
Definite CS (see Figure 3 for treatment)
Possible CS/Low probability of CS
Probable isolated CS (see Figure 3 for treatment)
No immunosuppression in most cases; evaluate for alternative diagnoses; consider repeat evaluation for CS if worsening symptoms
No immunosuppression in most cases; evaluate for alternative diagnoses; consider repeat evaluation for CS if worsening symptoms
Tissue diagnosis not available and CMR and PET together most consistent with sarcoidosis AND clinical manifestations of CS; would also consider genetic testing in this group
Does not meet clinical diagnostic criteria
Meets clinical diagnostic criteria
Possible CS/Low probability of CS
Probable CS (see Figure 3 for treatment)
No immunosuppression in most cases; evaluate for alternative diagnoses; consider repeat evaluation for CS if worsening symptoms


Unexplained sustained 2nd degree or 3rd degree AV block < 60y
High resolution CT chest
Advanced cardiac imaging (CMR or FDG-PET)
1. CT scan suggestive of pulmonary sarcoidosis
2. CMR or FDG-PET suggestive of CS
One or more of 1-2
Neither of 1-2
Positive – High probability of CS
Negative – Low probability
Consider alternative diagnosis
Biopsy
Extra-cardiac if feasible, otherwise
Guided EMB* to confirm diagnosis
Positive
Negative – Consider further biopsy and/or interval repeat imaging (especially if cardiac deterioration in follow-up)

CARDIAC SCREENING FOR EXTRACARDIAC SARCOIDOSIS

- HRS recommends: Cardiac History, ECG and Echo
- High index of suspicion with known extracardiac sarcoid
  - Further workup with cMRI and potentially PET
- HF Clinic

DIFFERENTIAL DIAGNOSIS

Differential Diagnosis

- Acute myocarditis/Giant Cell
- Chronic inflammatory cardiomyopathies (autoimmune, inherited, infiltrative)
- Arrhythmogenic cardiomyopathy (esp. desmoplakin variants)
- Cardiac amyloidosis

Key Diagnostic Challenges

- Overlapping features with myocarditis & inherited cardiomyopathies
- Young patients with arrhythmogenic phenotypes
- Imaging often insufficient for differentiation

Genetics & Reclassification

- Often reclassified as genetic cardiomyopathy
- 3-generation FH + Genetic testing

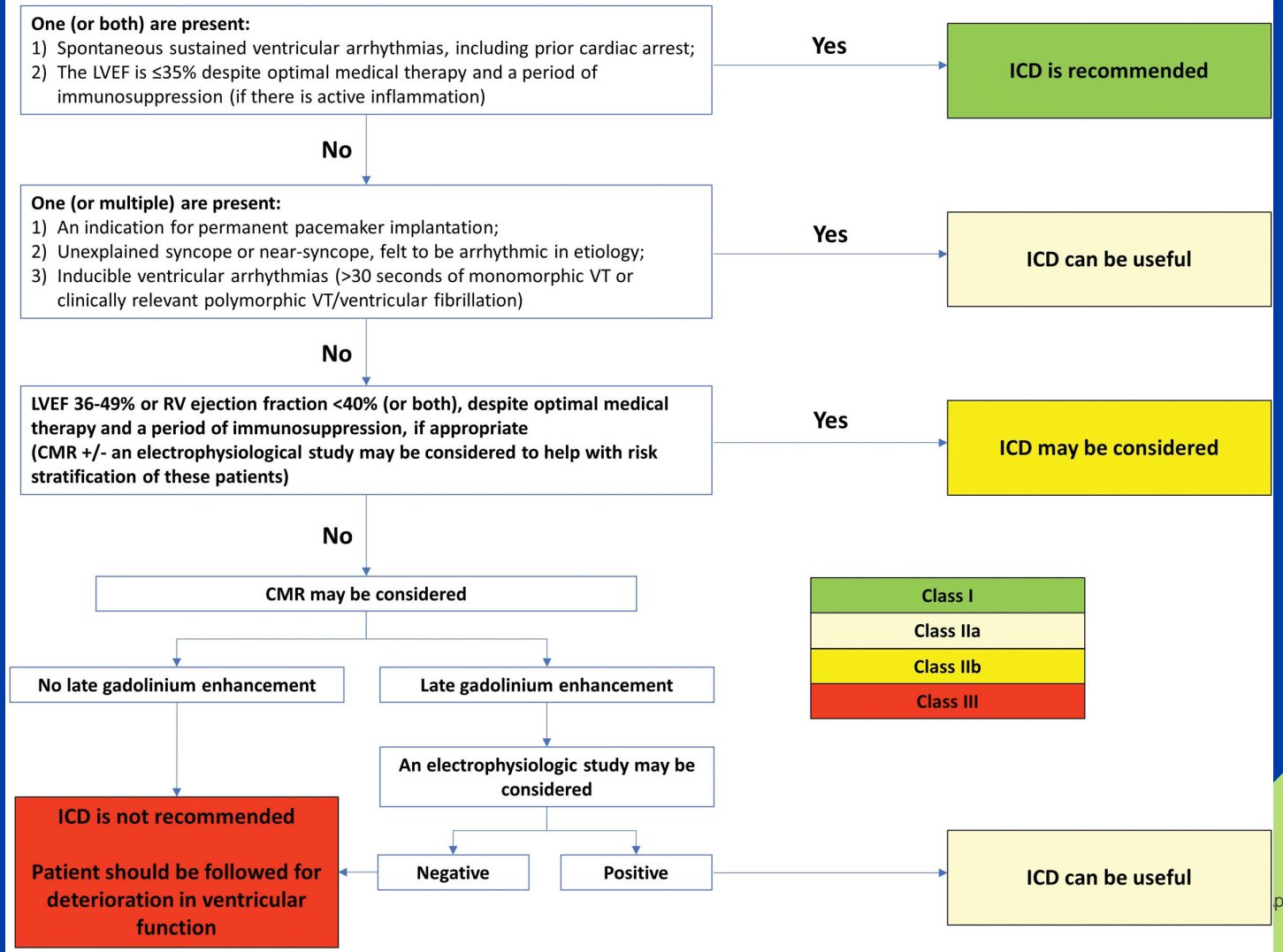
TREATMENT

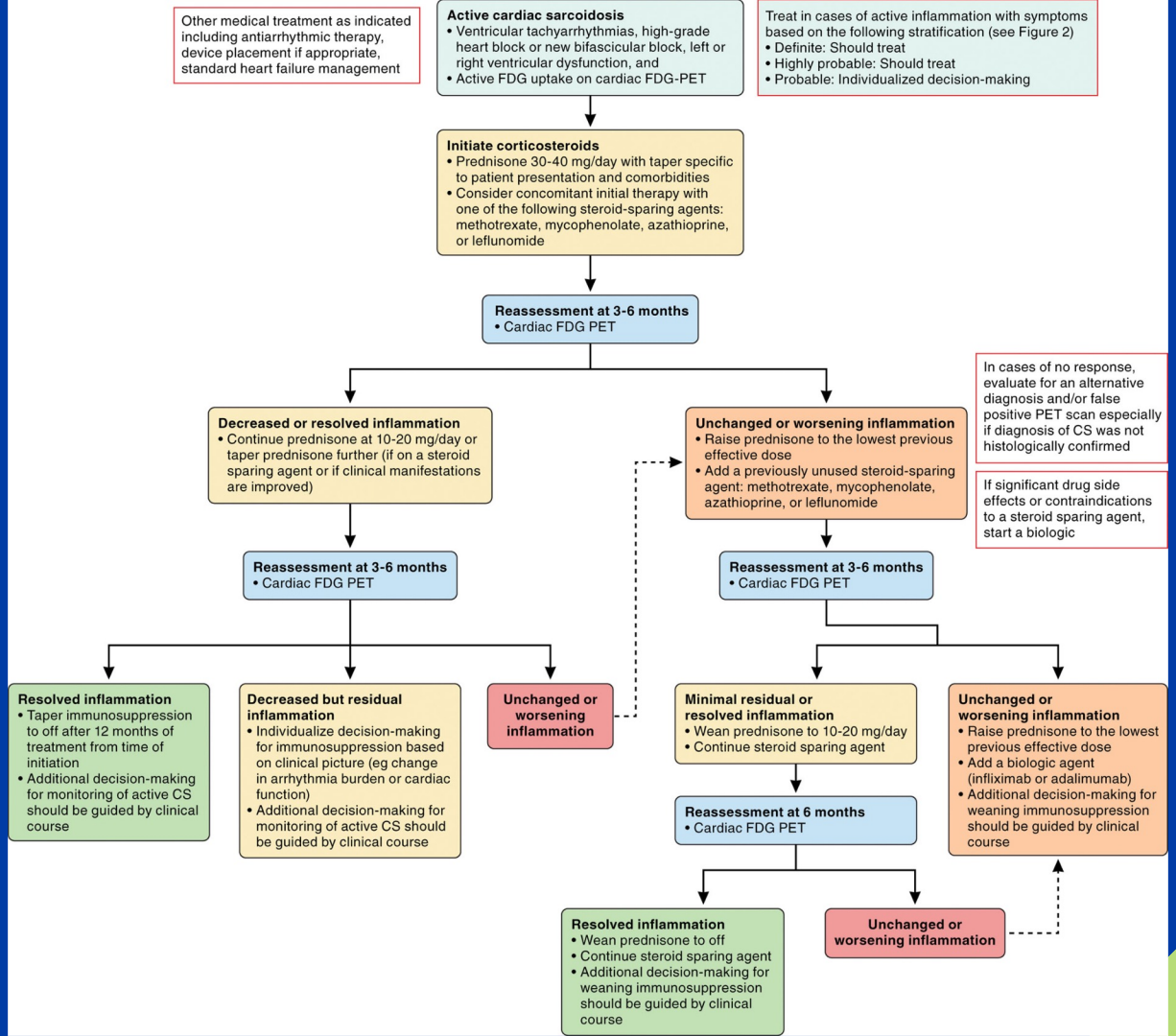
- ICD Therapy:

- IS:
  - Wide variation amongst institutions and disciplines
  - Typically steroids first line +/- steroid sparing agent
    - MTX, MMF, azothothioprine, TNF-alpha
  - Chasm-CS
    - Pred 0.5 mg/kg/day for 6 mnths vs. MTX + rapid pred taper (3 mnths)
    - PET: summed perfusion rest score (measure of myocardial fibrosis/scar)

- GDMT

- Advanced Therapies Considerations
  - RV involvement, VT, pHTN


One (or both) are present:
1) Spontaneous sustained ventricular arrhythmias, including prior cardiac arrest;
2) The LVEF is ≤35% despite optimal medical therapy and a period of immunosuppression (if there is active inflammation)
Yes
ICD is recommended
No
One (or multiple) are present:
1) An indication for permanent pacemaker implantation;
2) Unexplained syncope or near-syncope, felt to be arrhythmic in etiology;
3) Inducible ventricular arrhythmias (>30 seconds of monomorphic VT or clinically relevant polymorphic VT/ventricular fibrillation)
Yes
ICD can be useful
No
LVEF 36-49% or RV ejection fraction <40% (or both), despite optimal medical therapy and a period of immunosuppression, if appropriate
(CMR +/- an electrophysiological study may be considered to help with risk stratification of these patients)
Yes
ICD may be considered
No
CMR may be considered
No late gadolinium enhancement
Late gadolinium enhancement
An electrophysiologic study may be considered
Negative
Positive
ICD is not recommended
Patient should be followed for deterioration in ventricular function
ICD can be useful
Class I
Class IIa
Class IIb
Class III


Other medical treatment as indicated including antiarrhythmic therapy, device placement if appropriate, standard heart failure management
Active cardiac sarcoidosis
• Ventricular tachyarrhythmias, high-grade heart block or new bifascicular block, left or right ventricular dysfunction, and
• Active FDG uptake on cardiac FDG-PET
Treat in cases of active inflammation with symptoms based on the following stratification (see Figure 2)
• Definite: Should treat
• Highly probable: Should treat
• Probable: Individualized decision-making
Initiate corticosteroids
• Prednisone 30-40 mg/day with taper specific to patient presentation and comorbidities
• Consider concomitant initial therapy with one of the following steroid-sparing agents: methotrexate, mycophenolate, azathioprine, or leflunomide
Reassessment at 3-6 months
• Cardiac FDG PET
In cases of no response, evaluate for an alternative diagnosis and/or false positive PET scan especially if diagnosis of CS was not histologically confirmed
If significant drug side effects or contraindications to a steroid sparing agent, start a biologic
Decreased or resolved inflammation
• Continue prednisone at 10-20 mg/day or taper prednisone further (if on a steroid sparing agent or if clinical manifestations are improved)
Unchanged or worsening inflammation
• Raise prednisone to the lowest previous effective dose
• Add a previously unused steroid-sparing agent: methotrexate, mycophenolate, azathioprine, or leflunomide
Reassessment at 3-6 months
• Cardiac FDG PET
Reassessment at 3-6 months
• Cardiac FDG PET
Resolved inflammation
• Taper immunosuppression to off after 12 months of treatment from time of initiation
• Additional decision-making for monitoring of active CS should be guided by clinical course
Decreased but residual inflammation
• Individualize decision-making for immunosuppression based on clinical picture (eg change in arrhythmia burden or cardiac function)
• Additional decision-making for monitoring of active CS should be guided by clinical course
Unchanged or worsening inflammation
Minimal residual or resolved inflammation
• Wean prednisone to 10-20 mg/day
• Continue steroid sparing agent
Unchanged or worsening inflammation
• Raise prednisone to the lowest previous effective dose
• Add a biologic agent (infliximab or adalimumab)
• Additional decision-making for weaning immunosuppression should be guided by clinical course
Reassessment at 6 months
• Cardiac FDG PET
Resolved inflammation
• Wean prednisone to off
• Continue steroid sparing agent
• Additional decision-making for weaning immunosuppression should be guided by clinical course
Unchanged or worsening inflammation

TAKEAWAYS

- Red Flags: AV block <60 y/o, unexplained VT or cardiomyopathy
- Start with ECG and Echo; if clinical suspicion high cMRI w/ gadolinium
  Potentially followed by FDG-PET
- Pursue tissue diagnosis if possible prior to steroids
  Typically EBUS guided biopsy
- Recommend genetic testing
- Multiple treatment modalities, recommendations vary
- Multi-disciplinary approach