CARDIAC SARCOIDOSIS: CLINICAL FEATURES, DIAGNOSIS, AND MANAGEMENT

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I DEFINITION AND DUAL-PHASE PATHOPHYSIOLOGY

- **Definition (HRS 2014 / AHA 2024 / ESC 2023):** Cardiac Sarcoidosis (CS) is a multisystem granulomatous inflammatory disorder of unknown etiology characterized by the infiltration of **compact, non-caseating (non-necrotizing) epithelioid granulomas** (composed of activated macrophages, multinucleated giant cells, and CD4+ Th1/Th17 lymphocytes) primarily within the myocardium, interventricular septum, and conduction system.Clinically manifest in 5 percent of patients with systemic sarcoidosis, but present on autopsy or advanced imaging in **25 to 30 percent**, with up to 25 percent presenting as **clinically isolated cardiac sarcoidosis**.
- **Two Distinct Pathological Phases (Dictating Dual-Track Therapy):**
  - **Active Granulomatous Inflammatory Phase:** Focal granulomas and surrounding **myocardial edema** compress and interrupt the His-Purkinje system and trigger abnormal automaticity or triggered activity, causing **potentially reversible high-grade AV block**, polymorphic ventricular arrhythmias, and acute LV/RV dysfunction (**targeted by Immunosuppression**).
  - **Chronic Post-Inflammatory Fibrotic (Scar) Phase:** Healing via TGF-beta and fibroblast activation replaces myocardium with dense, patchy **collagen scar and ventricular aneurysms**, creating fixed anatomical slow-conduction channels that sustain **re-entrant Monomorphic Ventricular Tachycardia (MMVT)** and chronic heart failure (**targeted by ICD Implantation and Catheter Ablation**).

II CLINICAL FEATURES (THE CLASSIC TRIAD)

- **Conduction System Abnormalities (Most Common Initial Presentation — 30 to 45 Percent):**
  - **Hallmark: Complete (3rd-degree) or Mobitz Type II 2nd-degree Atrioventricular (AV) Block**, or new Right Bundle Branch Block / fascicular block, resulting from granulomatous infiltration of the **basal interventricular septum**.
  - **Clinical Red Flag: Idiopathic high-grade AV block in any young or middle-aged adult (<60 years of age)** is due to occult Cardiac Sarcoidosis in **15 to 30 percent of cases** and mandates pre-pacemaker CMR and/or 18F-FDG PET screening.
  - **Ventricular Tachyarrhythmias and Sudden Cardiac Death (SCD — ~30 Percent):** Frequent complex PVCs, non-sustained VT, **sustained monomorphic or polymorphic VT**, or **Sudden Cardiac Death** (which accounts for 30 to 65 percent of all deaths in CS and can be the very first presentation).
  - **Heart Failure and Cardiomyopathy Phenotypes (20 to 30 Percent):** Most commonly mimics **Dilated Cardiomyopathy (DCM)** with regional wall motion abnormalities, or presents as **Restrictive Cardiomyopathy**, **Right Ventricular failure mimicking ARVC**, or **ventricular aneurysms**. (Atrial arrhythmias occur in 20 to 30 percent due to atrial granulomas or LA dilation.)

III MULTIMODALITY DIAGNOSTIC ALGORITHM (HRS 2014 / JCS 2016 / AHA 2024)

- **Transthoracic Echocardiography (Screening Tool — Low Sensitivity in Early Disease):**
  - **Pathognomonic Hallmark: Thinning and akinesia/aneurysm of the basal anterior/inferior interventricular septum (wall thickness <4 mm)** or regional wall motion abnormalities in a **non-coronary distribution**, or focal basal septal thickening (>13 mm) during acute granulomatous edema, plus impaired **Global Longitudinal Strain (GLS)**.
  - **Cardiac Magnetic Resonance (CMR — Class I Anatomical Scar Reference):**
  - **Hallmark: Patchy, multifocal Late Gadolinium Enhancement (LGE)** most commonly in the **basal interventricular septum (often extending across the septum into both RV and LV free walls — the pathognomonic "Hook Sign")** and **subepicardial/mid-myocardial basal inferolateral wall** (sparing the subendocardium, though transmural LGE occurs in advanced scars).
  - **Prognostic Value:** Presence and extent of LGE (**especially LGE >10 to 20 percent of LV mass or any RV LGE**) is the single strongest independent predictor of **VT and Sudden Cardiac Death**, even when LVEF is completely normal (>50 percent).
  - **Cardiac 18F-FDG PET/CT + Perfusion Imaging (Class I Metabolic Inflammation Reference):**
  - **Mandatory Preparation: 24-to-48-hour high-fat, zero-carbohydrate diet + 12-to-18-hour fast (+ IV unfractionated heparin 50 IU/kg)** to suppress physiological cardiomyocyte glucose uptake.
  - **Hallmark: Focal or focal-on-diffuse myocardial 18F-FDG uptake** colocalized with a **resting Rb-82 / N-13 ammonia perfusion defect ("Perfusion-Metabolism Mismatch")**, alongside FDG-avid **bilateral hilar or mediastinal lymphadenopathy** (which provides a high-yield target for **EBUS-guided biopsy**).
  - **Histological Confirmation (Extracardiac Biopsy vs. Guided Endomyocardial Biopsy):**
  - **HRS 2014 Pathways:** Diagnosis is established either by (A) **Direct Endomyocardial Biopsy (EMB)** showing non-caseating granulomas (note: blind RV apical EMB has a sensitivity of **only 20 to 25 percent** due to patchy basal/LV distribution, which doubles to **~50 percent when guided by intra-procedural 3D Electroanatomical Voltage Mapping** targeting fractionated low-voltage border zones [1.5–0.5 mV] or PET/CMR imaging), OR (B) **Clinical Pathway:** Histological proof of **extracardiac sarcoidosis** (via EBUS mediastinal node, lung, or skin biopsy) **plus** compatible cardiac imaging (CMR LGE or PET uptake) and clinical features (AV block, VT, or steroid-responsive cardiomyopathy).

Diagnostic / Therapeutic Domain	Primary Modality / Intervention	Specific Guideline Criterion / Action (HRS 2014 / ESC 2022 / AHA 2024)
Active Myocardial Inflammation	**Cardiac 18F-FDG PET/CT** (with high-fat/fasting prep)	Dictates **Immunosuppression (Class I/IIa): Prednisone (0.5 mg/kg/d or 30–40 mg/d)** + early **Methotrexate** (repeat PET at 3–6 mo to guide taper)
Arrhythmogenic Fibrotic Scar	**Cardiac MRI with LGE**	Dictates **Sudden Death Protection (ICD):** High SCD risk persists even after PET inflammation resolves (**ILLUMINATE-CS**)
ICD Class I Indications	Secondary prevention or severe HFrEF	(1) **Sustained VT or Aborted Cardiac Arrest**; OR (2) **LVEF <= 35%** despite optimal medical therapy and immunosuppression

Diagnostic / Therapeutic Domain	Primary Modality / Intervention	Specific Guideline Criterion / Action (HRS 2014 / ESC 2022 / AHA 2024)
ICD Class IIa Indications (The "Low-Threshold" Rules)	Primary prevention with LVEF >35%	(1) **ANY indication for permanent pacing (e.g., high-grade/Complete AV Block)** -> implant **ICD instead of pacemaker** regardless of LVEF; (2) **Significant LGE on CMR** (ESC 2022 / ACC-AHA 2017); (3) Unexplained syncope; or (4) **Inducible sustained VT on EPS** (LVEF 36–49% and/or RVEF <40% alone is IIb in HRS 2014)

IV GUIDELINE-DIRECTED MANAGEMENT (IMMUNOSUPPRESSION, DEVICES, AND ABLATION)

- **Immunosuppressive Therapy (Indicated for Active FDG-PET Inflammation + AV Block, VT/PVCs, or LV/RV Dysfunction):**
  - **First-Line Corticosteroids (Class I / IIa): Oral Prednisone / Prednisolone at 0.5 mg/kg/day (typically 30 to 40 mg/day)** (contemporary practice favours 30 to 40 mg/day over historical 60 mg/day dosing to limit weight gain and diabetes; the randomized **CHASM-CS-RCT** is still enrolling). Reverses Mobitz II / complete AV block in **~40 to 50 percent of patients** (versus 0 percent spontaneous recovery in untreated CS) and preserves LVEF.
  - **Early Steroid-Sparing Second-Line Agents (Class IIa): Methotrexate (10 to 20 mg once weekly + folic acid)** (preferred first-line steroid sparer), **Mycophenolate Mofetil**, **Azathioprine**, or **Leflunomide** initiated upfront or early to enable steroid tapering over 6 to 12 months and prevent relapse (which occurs in 30 to 40% upon stopping steroids alone).
  - **Third-Line Biologics for Refractory CS: TNF-Alpha Inhibitors — Infliximab (5 mg/kg IV at Weeks 0, 2, 6, then every 4–8 weeks) or Adalimumab** are effective in steroid/methotrexate-refractory active disease (after strictly excluding latent/active **Tuberculosis** and adjusting for severe NYHA IV heart failure).
  - **Serial FDG-PET Monitoring:** Repeat **Cardiac 18F-FDG PET at 3 to 6 months** after starting therapy to confirm metabolic resolution before tapering corticosteroids.
  - **Antiarrhythmic Drugs and Catheter Ablation:**
  - **Medical Suppression: Amiodarone** or **Sotalol** (plus Beta-blockers) are used for recurrent VT; **Class IC Sodium Channel Blockers (Flecainide, Propafenone) are strictly contraindicated (Class III)** due to myocardial scar and proarrhythmia.
  - **Catheter Ablation (Class IIa for Refractory VT):** Performed **only after active myocardial inflammation has been suppressed with immunosuppression** (ablating acutely edematous, inflamed myocardium has high failure and recurrence rates) and frequently requires **combined endocardial and percutaneous epicardial mapping/ablation** due to deep intramural/subepicardial RV and LV scars.

V LANDMARK REGISTRIES AND CLINICAL TRIALS

- **ILLUMINATE-CS Registry (Nabeta et al., *Eur Heart J* 2022; n = 512):** Japanese multicentre registry showing a high long-term arrhythmic risk (estimated **10-year fatal ventricular arrhythmia rate ~32 percent**, composite of death, HF hospitalization or fatal arrhythmia ~48 percent), supporting the principle that **PET guides immunosuppression while CMR LGE and LVEF guide ICD implantation**.
- **CHASM-CS-RCT (Birnie et al., Ongoing Randomized Trial):** Compares **low-dose Prednisone + Methotrexate** with **standard-dose Prednisone monotherapy** in newly diagnosed active CS, testing whether early steroid-sparing therapy is non-inferior with less corticosteroid toxicity; results are awaited.

KEY REFERENCES

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- **Zeppenfeld K, Tfelt-Hansen J, de Riva M, et al.:** 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death, *European Heart Journal*, 2022.
- **Nabeta T, Kitai T, Naruse Y, et al. (ILLUMINATE-CS Investigators):** Risk stratification of patients with cardiac sarcoidosis: the ILLUMINATE-CS registry, *European Heart Journal*, 2022.