GRANULOMATOUS MYOCARDITIS: CURRENT STATUS

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I CORE CONCEPTS AND CLASSIFICATION

- **Definition:** Granulomatous myocarditis comprises a distinct group of inflammatory myocardial disorders characterized histopathologically by granulomatous inflammation or multinucleated giant cells, presenting with a disproportionally high incidence of **high-grade atrioventricular (AV) block, malignant ventricular tachyarrhythmias, and progressive or fulminant heart failure**.
- **Primary Non-Infectious ("Two Giants") Etiologies:**
  - **Cardiac Sarcoidosis (CS):** Characterized by **well-formed, discrete, compact non-caseating (non-necrotizing) epithelioid granulomas** with Langhans/foreign-body giant cells, CD4+ T-helper lymphocytes, and dense replacement fibrosis. Clinically manifest in 5 percent of systemic sarcoidosis patients, but present on autopsy/imaging in **25 to 30 percent**, and up to 25 percent of CS cases present as **clinically isolated cardiac sarcoidosis**.
  - **Idiopathic Giant Cell Myocarditis (GCM):** Characterized by a **diffuse, serpiginous mixed inflammatory infiltrate** (CD8+ T-lymphocytes, **abundant eosinophils**, and macrophages) with **prominent multinucleated giant cells at the margins of extensive myocyte necrosis, in the absence of well-formed granulomas**. Note: Although classically grouped alongside CS in exam differentials due to giant cells, GCM is strictly a **non-granulomatous** necrotizing giant-cell myocarditis.
  - **Infectious, Autoimmune, and Drug-Induced Granulomatous Causes: Tuberculous Myocarditis** (**caseating/necrotizing granulomas** with acid-fast bacilli), fungal myocarditis (*Histoplasma, Cryptococcus, Aspergillus*), parasitic (*Trypanosoma, Toxoplasma*), **Acute Rheumatic Fever** (pathognomonic perivascular **Aschoff bodies** with **Anitschkow "caterpillar" histiocytes**), **Granulomatosis with Polyangiitis (GPA)**, and drug hypersensitivity.

II CARDIAC SARCOIDOSIS (CS): DIAGNOSIS AND MANAGEMENT (HRS 2014 / JCS 2016 / AHA 2024 / ESC 2025)

- **Classic Clinical Triad:** (1) **Conduction System Disease** (most common initial manifestation: complete **AV block** or Mobitz II in **30 to 45 percent** of cases, particularly in adults **under 60 years of age**, or new RBBB); (2) **Ventricular Arrhythmias** (sustained monomorphic/polymorphic **VT** or sudden cardiac death from scar re-entry and active inflammation); and (3) **Heart Failure** (HFrEF, restrictive cardiomyopathy, or **basal interventricular septal thinning [less than 4 mm]** / ventricular aneurysms mimicking ARVC or ischemic CAD).
- **Diagnostic Criteria (HRS 2014 vs. Japanese Circulation Society [JCS] 2016):**
  - **HRS 2014 Criteria:** Requires either (1) **Histological Diagnosis from Myocardial Tissue** (non-caseating granuloma on **Endomyocardial Biopsy [EMB]**; note that unguided RV biopsy has a sensitivity of only **20 to 25 percent** due to patchy basal/left-sided involvement, increasing to **50 percent with electroanatomical voltage-mapping or CMR/PET guidance**), OR (2) **Clinical Diagnosis** (histological proof of **extracardiac sarcoidosis** [e.g., EBUS-guided mediastinal lymph node biopsy] **plus** one or more cardiac criteria: steroid-responsive cardiomyopathy/AV block, unexplained LVEF less than 40 percent, unexplained sustained VT, Mobitz II or 3rd-degree AV block, patchy uptake on **18F-FDG PET**, **Late Gadolinium Enhancement [LGE] on CMR**, or positive Gallium-67 uptake).
  - **JCS 2016 Criteria:** Uniquely permits a clinical diagnosis of **Isolated Cardiac Sarcoidosis** using multimodality imaging (CMR + 18F-FDG PET + clinical majors) even when extracardiac biopsy is negative.
  - **Multimodality Imaging Paradigm (Class I):**
  - **Cardiac MRI (CMR):** Identifies **myocardial scar/fibrosis** via **patchy, multifocal, non-coronary Late Gadolinium Enhancement (LGE)**, classically involving the **basal interventricular septum (RV and LV sides — the "hook sign")**, subepicardial/mid-myocardial LV lateral wall, and RV free wall. Presence of LGE (especially involving greater than 10 to 20 percent of LV mass or the RV) is the strongest predictor of VT and sudden death even when LVEF is preserved (greater than 50 percent).
  - **Cardiac 18F-FDG PET/CT (After Strict 24-Hour High-Fat, Zero-Carbohydrate Diet + 12-to-18-Hour Fast with IV Unfractionated Heparin):** Suppresses physiological myocardial glucose uptake so that **focal or focal-on-diffuse 18F-FDG uptake** paired with **resting Rb-82/N-13 ammonia perfusion defects ("perfusion-metabolism mismatch")** identifies **active macrophage-driven myocardial inflammation**, guides biopsy, and serially monitors immunosuppression response.
  - **Management of Cardiac Sarcoidosis:**
  - **Immunosuppression (Class I/IIa for Active Inflammation with AV Block, VT, or LV Dysfunction): Corticosteroids** (**Prednisolone 0.5 mg/kg/day**, typically **30 to 40 mg/day**—shown in contemporary registries to be as effective and safer than historical 60 mg/day dosing—slowly tapered over 6 to 12 months guided by repeat **FDG-PET** at 3 to 6 months). Early initiation of **steroid-sparing second-line agents** (**Methotrexate 10 to 20 mg weekly** with folic acid, **Mycophenolate Mofetil**, or **Azathioprine**) reduces relapse and steroid toxicity, while **TNF-alpha inhibitors (Infliximab or Adalimumab)** are used for refractory disease.
  - **Lower Threshold for ICD Implantation (HRS 2014 / ESC 2022 VA-SCD / ACC-AHA-HRS):** Because CS carries a high rate of fatal ventricular arrhythmias even with preserved or mildly reduced LVEF, an **ICD is Class I indicated** for secondary prevention (sustained VT/cardiac arrest) or **LVEF 35 percent or less**; importantly, **ICD implantation is Class IIa recommended whenever a permanent pacemaker is indicated for high-grade AV block in CS (even if LVEF is normal)**, when **significant LGE persists on CMR after the acute inflammatory phase** (ESC 2022), or when **sustained VT is inducible on EP study**, and may be considered (Class IIb) when **LVEF is 36 to 49 percent or RVEF is less than 40 percent** despite immunosuppression (HRS 2014).

III GIANT CELL MYOCARDITIS (GCM): THE FULMINANT THREAT

- **Pathophysiology and Autoimmune Associations:** A fulminant, T-lymphocyte-mediated necrotizing autoimmune myocarditis; **20 percent of cases occur in patients with coexisting autoimmune disorders** (**ulcerative colitis/Crohn disease, thymoma, myasthenia gravis, autoimmune thyroiditis, or pernicious anemia**).
- **Clinical Course:** Rapidly progressive **fulminant heart failure/cardiogenic shock (75 percent)**, **incessant refractory ventricular arrhythmias (50 percent)**, and/or **high-grade AV block** over days to weeks in previously healthy young-to-middle-aged adults. Untreated median transplant-free survival is less than **3 months**.
- **Mandatory Endomyocardial Biopsy (Class I, Level B):** Urgent **Endomyocardial Biopsy (EMB)** is **Class I mandatory** in any patient presenting with unexplained new-onset heart failure of less than 2 weeks' duration with hemodynamic compromise, or 2 weeks to 3 months' duration associated with a dilated LV and **new ventricular arrhythmias or Mobitz II / 3rd-degree AV block**, or failure to respond to usual care within 1 to 2 weeks. Because GCM inflammation is diffuse, **EMB sensitivity in GCM is high (80 to 85 percent)** (rising above 90 percent on repeat biopsy).
- **Combined Cyclosporine-Based Triple Immunosuppression:** Unlike lymphocytic myocarditis, GCM responds to immediate **multi-agent T-cell immunosuppression**—combining **Cyclosporine** (target trough 100 to 200 ng/mL, or **Tacrolimus**), **High-Dose Intravenous Methylprednisolone** (1000 mg/day for 3 days followed by oral Prednisone 1 mg/kg/day), and **Antithymocyte Globulin (ATG)**, historically **Muromonab-CD3 (now withdrawn)**, **Alemtuzumab**, **Mycophenolate Mofetil**, or **Azathioprine**—which extends median transplant-free survival from 3 months to **over 11 to 12 months** (with 5-year transplant-free survival of 50 to 70 percent), alongside early **VA-ECMO / Impella / biventricular VAD** support as a bridge to recovery or **Heart Transplantation** (note: GCM can recur in 20 to 25 percent of transplanted donor hearts, usually responding to augmented immunosuppression).

IV DISTINGUISHING CARDIAC SARCOIDOSIS FROM GIANT CELL MYOCARDITIS

Clinical / Pathological Feature	Cardiac Sarcoidosis (CS)	Idiopathic Giant Cell Myocarditis (GCM)
Clinical Tempo & Presentation	Subacute to chronic (weeks to years); **AV block (most common)**, VT, progressive HF	**Fulminant / Hyperacute** (days to weeks); cardiogenic shock, incessant VT storm, AV block
Histopathology on EMB	**Well-formed, compact non-caseating granulomas**; dense fibrosis; minimal myocyte necrosis or eosinophils	**Diffuse serpiginous myocyte necrosis**, **prominent eosinophils**, CD8+ T-cells, and **multinucleated giant cells WITHOUT organized granulomas**
Unguided RV EMB Sensitivity	**Low (20–25%)** due to patchy basal/LV distribution (improves to ~50% with voltage/imaging guidance)	**High (80–85%)** due to diffuse subendocardial involvement
First-Line Immunosuppression	**Corticosteroids (Prednisolone 30–40 mg/d)** +/- **Methotrexate** or Mycophenolate (Infliximab if refractory)	**Calcineurin-Inhibitor Triple Therapy: Cyclosporine (or Tacrolimus) + High-Dose Steroids + ATG / Azathioprine / MMF**
Prognosis & MCS/Transplant	5-year survival **>85–90%** with immunosuppression + ICD	Untreated median survival **<3 months**; 5-yr transplant-free survival **50–70%** with Cyclosporine + MCS

V PRACTICAL CONSIDERATIONS IN THE INDIAN CLINICAL CONTEXT

- **The "Tuberculosis vs. Cardiac Sarcoidosis" Diagnostic Dilemma:** In India, **Mycobacterium tuberculosis** is a major cause of mediastinal lymphadenopathy and granulomatous myocarditis/pericarditis. Because both TB and Sarcoidosis present with hilar/mediastinal lymphadenopathy, basal myocardial LGE, and FDG-PET avidity—and high-dose corticosteroids/infliximab can precipitate fatal disseminated tuberculosis—every suspected Indian CS patient requires **EBUS-TBNA of FDG-avid mediastinal nodes** tested for **caseating necrosis, AFB staining, Xpert MTB/RIF Ultra, and liquid MGIT mycobacterial culture**, alongside **Tuberculin Skin Test / IGRA (QuantiFERON-TB Gold)** and High-Resolution Chest CT. In indeterminate overlapping cases ("tuberculous sarcoidosis"), concurrent or upfront anti-tubercular therapy (ATT) alongside steroid therapy is frequently practiced in Indian tertiary centers.
- **Strict Dietary Preparation for Cardiac 18F-FDG PET/CT:** In Indian patients with high habitual carbohydrate intake (rice/wheat), inadequate dietary preparation causes diffuse physiological LV FDG uptake that masks or mimics active sarcoidosis; strict enforcement of a **24-to-48-hour high-fat, zero-carbohydrate diet** followed by a **12-to-18-hour fast** (plus intravenous unfractionated heparin 50 IU/kg 15 minutes before FDG injection) is essential for diagnostic PET accuracy.
- **ICD Over Standalone Pacemaker in Young Indian Adults with Complete Heart Block:** Up to **15 to 25 percent of idiopathic complete heart block in young-to-middle-aged Indian adults (aged 18 to 60 years)** is secondary to occult **Cardiac Sarcoidosis** (or TB myocarditis); performing a **CMR or FDG-PET prior to pacing** is critical because confirming CS upgrades the device indication from a simple dual-chamber pacemaker to a **dual-chamber ICD (Class IIa)**.

KEY REFERENCES

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