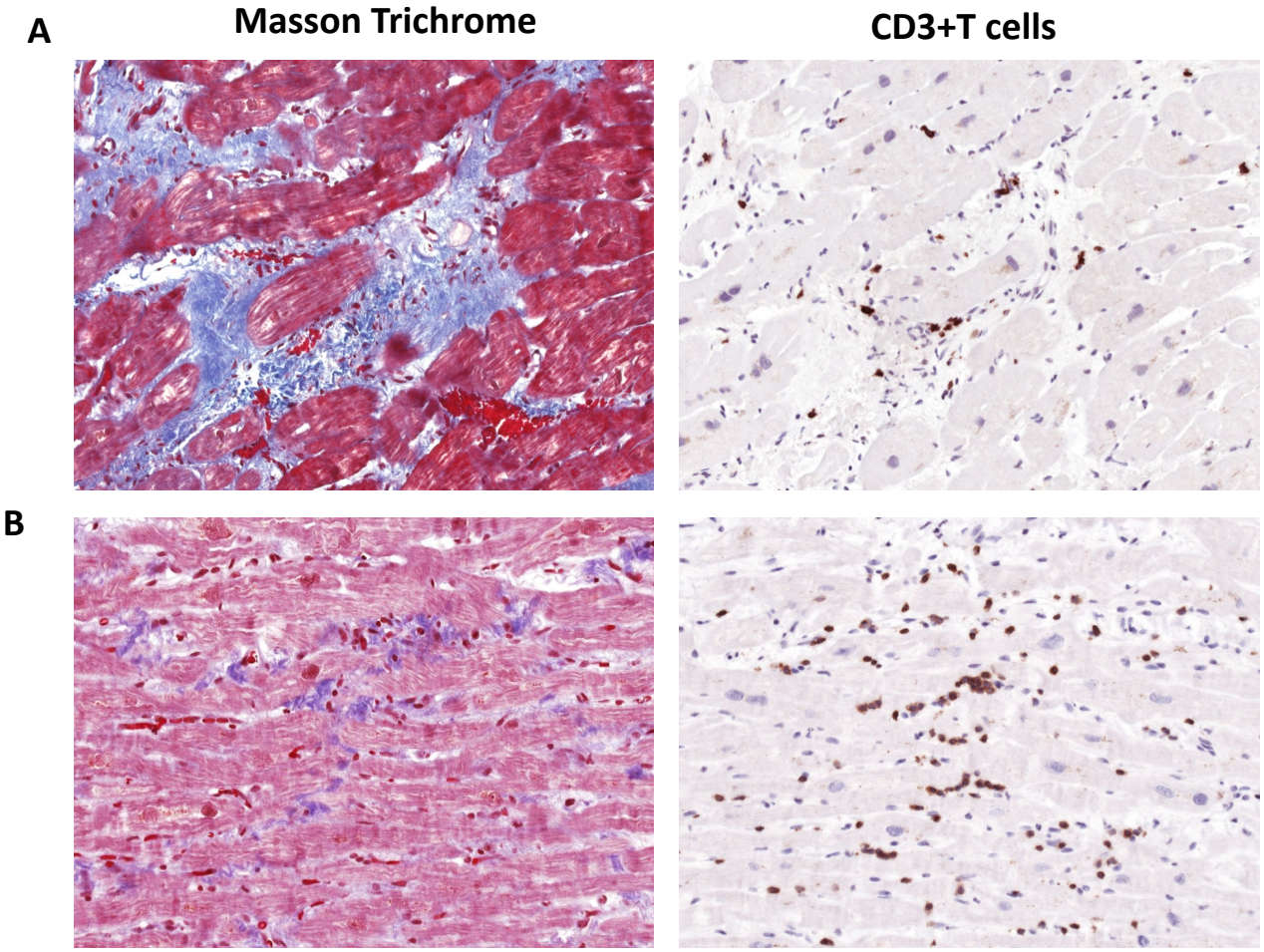
SUPPLEMENTAL MATERIALS

MANAGEMENT OF ACUTE MYOCARDITIS AND CHRONIC INFLAMMATORY CARDIOMYOPATHY: AN EXPERT CONSENSUS DOCUMENT

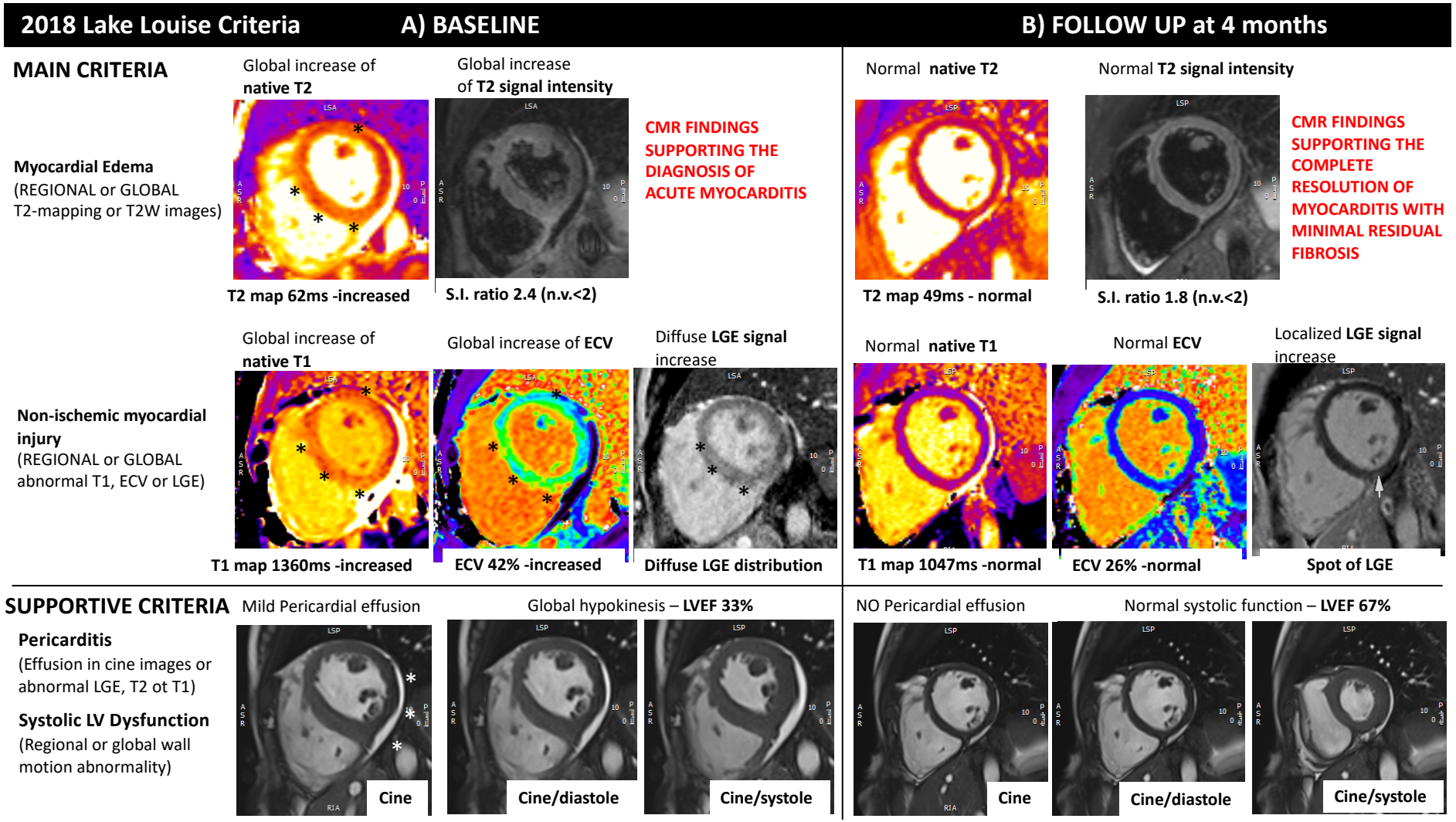
Ammirati et al. **Management of myocarditis**

SUPPLEMENTAL FIGURES

SUPPLEMENTAL FIGURE I.



SUPPLEMENTAL FIGURE II.



SUPPLEMENTAL FIGURE LEGENDS:

SUPPLEMENTAL FIGURE I. Different histological findings in chronic inflammatory cardiomyopathy vs. chronic lymphocytic myocarditis. (A) Chronic Inflammatory cardiomyopathy in a 56-year-old man reveals significant variations of myocyte diameter (but no myocyte necrosis), interstitial and focal replacement type fibrosis with associated inflammation. **(B) Chronic lymphocytic myocarditis** in a 48-year-old woman is morphologically characterized by a diffuse interstitial fibrosis and immune cell infiltrates in absence of myocyte necrosis (Left side: Masson Trichrome stain; right side CD3+ T cell immunohistochemistry, magnitude x200).

SUPPLEMENTAL FIGURE II. Updated cardiac magnetic resonance (CMR) criteria to support the diagnosis of acute myocarditis and to track myocardial tissue changes over time. The images are from a 32-year old female patient admitted to hospital with fulminant myocarditis, needing inotropes and intra-aortic balloon pump during the acute phase. Endomyocardial biopsy showed diffuse lymphocytic infiltrates with myocardial necrosis. The patient was treated with methylprednisolone. CMR at 1.5 T was acquired when the patient was hemodynamically stable at baseline **(A)** within 2 weeks from the onset of cardiac symptoms and **(B)** after 4 months of follow up. In **A** main 2018 Lake Louise Criteria (LLC) criteria are fulfilled, as both signs of myocardial edema and non-ischemic inflammatory injury are present. T2-weighted (T2W) imaging shows increased T2 values at T2-mapping (T2=64 ms) and increased myocardial/skeletal muscle signal (SI) intensity ratio at STIR T2-weighted images (SI ratio=2.4). Myocardial injury is also evident based on very elevated native T1 (=1360 ms) and extracellular volume (ECV) expansion (42%); post-contrast images show global late gadolinium enhancement (LGE); all the findings are more evident in the septum (*). Supportive criteria are also present: a small pericardial effusion is evident at cine images and there is global hypokinesis (left ventricular ejection fraction [LVEF] of 33%, see **SUPPLEMENTAL VIDEO 1**). All findings are consistent with severe global myocardial inflammation. In **B**, follow-up images at 4 months are shown. Compared to the scan acquired in the acute phase, both signs of edema and of non-ischemic injury are significantly reduced. Native T2 at T2 mapping has decreased to 49 ms and SI ratio at STIR T2-weighted images is 1.8. The values of native T1 and ECV are significantly reduced (1047 ms and 26%, respectively), and there is only a small spot of LGE (arrow) in the septum. The pericardial effusion has resolved, and ventricular function has normalized (LVEF 67%, see **SUPPLEMENTAL VIDEO 2**). Of note, wall thickness has also normalized. Increased wall thickness and mass in the acute phase can represent an indirect sign of myocardial edema. T1 and T2 mapping results should be evaluated according to CMR laboratory reference values.

SUPPLEMENTAL TABLES:

Supplemental TABLE I. Autoptic series assessing the prevalence of myocarditis among sudden cardiac death in young people.

M indicates male; N numbers; NA not available; y years.

First Author	Years	Country	N autopsy	Age; Male sex (%)	Type of population	Proportion of myocarditis	Among myocarditis Age; Male sex (%)	Death at rest vs. During effort	Notes
Corrado et al.[4] 2001	1979-1998	Italy	273	24y; 80% M	Veneto Region of Italy, prospective collection of sudden deaths ≤35y	10% (n=27)	21 y; 74% M	At rest 21 (78%), of whom 2 during sleep. During effort in 6 (22%) of whom 3 competitive athletes	The most frequent substrate in those victims with apparently normal heart. Patchy interstitial inflammatory infiltrates in all cases. Most frequent histology: polymorphous infiltrate (59%), lymphocytic (33%) and giant cell (4%).
Eckart et al.[119] 2011		USA	298	26y; 95%	Department of Defense	5.7% (n=17)	NA	Non-exertional 12 (71%)	-

					Cardiovascular Death Registry of sudden deaths ≤35y			Exertional 5 (29%)	
Harmon et al.[5] 2014	2004-2008	USA	36	NA	National Collegiate Athletic Association	8% (n=3)	NA	NA	-
Maron et al.[120] 2016	1980-2011	USA	842	19y; 89% M	United States National Registry. Young competitive athletes	7% (n=57) Sarcoidosis: 0.5% (n=4)	17 y; 81% M Sarcoidosis: 26 y; 100% M	NA	In Whites 52%; in African American 42% Sarcoidosis: In African American 75%, in Whites 25%
Lynge et al.[121] 2019	2000-2009	Denmark	753 (82% forensic autopsies; 18% hospital autopsies)	NA	Nationwide study, deaths in people aged 1-49y	6% (n=42)	31 y; 69% M	At rest 38 (91%) of whom 18 during sleep. During activity 2 (5%), the remaining ones not specified	Diagnosis of myocarditis required confirmation by histopathology according to the Dallas criteria which includes the presence of inflammatory infiltrates

									with/or without myocyte necrosis. Postmortem virology examination on myocardial tissue specimen performed in 10 (24%) with a positive result in 30% (2 cases of parvovirus B19 and one case with missing information on virus type)

Supplemental TABLE II. Diagnostic targets for cardiac magnetic resonance (CMR).

EF indicates ejection fraction; ECV, Extracellular volume; LGE, late gadolinium enhancement; LV, left ventricular; RV, right ventricular.

Target	Technique	Recommended parameters
Global Function	Cine CMR	LV-EF, global longitudinal strain, LV stroke volume index, LV end-diastolic and systolic volume index, RV volumes and EF, RV stroke volume index, RV end-diastolic and systolic volume index,
Regional Function	Cine CMR	Regional wall thickening, regional strain
Edema	Water-sensitive CMR (T2 mapping, T2-weighted images)	Location and extent of edema (myocardial T2, T2 signal intensity ratio)
Necrosis, scar	LGE CMR, T1 mapping	Location and extent of necrosis (signal intensity in LGE images or myocardial T1)
Diffuse fibrosis	T1 mapping	ECV, increased myocardial T1
Pericarditis	Cine, LGE	Extent and location of pericardial inflammation (signal intensity in LGE images) and effusion (visible fluid)

Supplemental TABLE III. Expert Consensus Recommendations on Cardiac Sarcoidosis

Modified from Birnie et al. (Heart Rhythm. 2014;11:1305-1323).

CMR indicates cardiac magnetic resonance; CS, cardiac sarcoidosis; ECG, electrocardiogram; FDG-PET, fluorodeoxyglucose-positron emission tomography; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction.

Diagnosis and Screening	
It is recommended that patients with biopsy-proven extracardiac sarcoidosis should be asked about unexplained syncope/presyncope/significant palpitations.	I
It is recommended that patients with biopsy-proven extracardiac sarcoidosis should be screened for cardiac involvement with a 12-lead ECG.	I
Screening for cardiac involvement with an echocardiogram can be useful in patients with biopsy-proven extracardiac sarcoidosis.	IIa
Advanced cardiac imaging—CMR or FDG-PET—at a center with experience in CS imaging protocols can be useful in patients with one or more abnormalities detected on initial screening by symptoms/ECG/echocardiogram.	IIa
Screening for CS in patients <60 years of age with unexplained second-degree (Mobitz type II) or third-degree atrioventricular block can be useful.	IIa
Advanced cardiac imaging—CMR or FDG-PET—is not recommended for patients without abnormalities on initial screening by symptoms/ECG/echocardiogram.	III
Management of Conduction Abnormalities	
Device implantation can be useful in CS patients with an indication for pacing, even if the atrioventricular block reverses transiently.	IIa
Immunosuppression can be useful in CS patients with second-degree (Mobitz II) or third-degree atrioventricular block.	IIa
ICD implantation can be useful in patients with CS and an indication for permanent pacemaker implantation.	IIa
Management of Ventricular Arrhythmias	
Assessment of myocardial inflammation with FDG-PET can be useful in CS patients with ventricular arrhythmias.	IIa

Immunosuppression can be useful in CS patients with ventricular arrhythmias and evidence of myocardial inflammation.	IIa
Antiarrhythmic drug therapy can be useful in patients with ventricular arrhythmias refractory to immunosuppressive therapy.	IIa
Catheter ablation can be useful in patients with CS and ventricular arrhythmias refractory to immunosuppressive *AND* antiarrhythmic therapy.	IIa
Risk Stratification for Sudden Cardiac Death	
An electrophysiological study for the purpose of sudden death risk stratification may be considered in patients with LVEF >35%, despite optimal medical therapy and a period of immunosuppression (if there is active inflammation).	IIb
CMR for the purpose of sudden death risk stratification may be considered.	IIb
Implantable Cardioverter-Defibrillator Implantation	
Spontaneous sustained ventricular arrhythmias, including prior cardiac arrest.	I
LVEF ≤35% despite optimal medical therapy and a period of immunosuppression (if there is active inflammation).	I
ICD implantation can be useful in patients with CS, independent of ventricular function and one or more of the following: 1. An indication for permanent pacemaker implantation; 2. Unexplained syncope or near-syncope, felt to be arrhythmic in etiology; and 3. Inducible sustained ventricular arrhythmias.	IIa
ICD implantation may be considered in patients with LVEF 36-49% and/or RVEF <40%, despite optimal medical therapy for heart failure and a period of immunosuppression (if there is active inflammation).	IIb

SUPPLEMENTAL REFERENCES 101-121

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