Acute Cardiovascular Complications of Immune-Mediated Systemic Inflammatory Diseases

Brittany N. Weber, MD, PhD¹, Micheal Garshick, MD², Antonio Abbate, MD, PhD³, Taryn Youngstein, MD⁴, Garrick Stewart, MD¹, Erin Bohula, MD¹, Sven Plein, MD, PhD⁵, Monica Mukherjee, MD, MPH⁶

Author Affiliations
1. Brigham and Women's Hospital, Harvard Medical School, Boston, MA
2. NYU Langone Medical Center, New York City, NY
3. University of Virginia School of Medicine, Charlottesville, VA
4. Imperial College London, UK
5. University of Leeds, Leeds, UK
6. Johns Hopkins University School of Medicine, Baltimore, MD

Funding: BNW: NIH/NHLBI K23HL159276, American Heart Association 21CDA851511; MM: NIH/NHLBI R01HL162851, National Scleroderma Foundation

Disclosures: AA: Scientific Advisory Board for Kiniksa, Implicit Biosciences, Novo Nordisk, Olatec, R-Pharm; MM: Data Safety Monitoring Board, Advarra, Inc. BW: Scientific Advisory Board, Novo Nordisk, Kiniksa, Horizon Therapeutics. MG: Kiniksa, Horizon Therapeutics

Abstract
Immune-mediated systemic inflammatory conditions (IMIDs) are associated with an increased risk of atherosclerosis and adverse cardiovascular (CV) events secondary to pathogenic inflammation and derangements in the innate and adaptive immune responses inherent to the underlying rheumatic diseases. As the intersection of cardio-rheumatology continues to expand, a multidisciplinary approach must be considered to optimize clinical outcomes and long-term survival. This review will highlight acute cardiac manifestations of systemic inflammatory diseases and propose a clinically relevant framework for diagnosis, management, and the role of integrated multimodality imaging.

© The Author(s) 2023. Published by Oxford University Press on behalf of the European Society of Cardiology. All rights reserved. For permissions, please e-mail: journals.permissions@oup.com This article is published and distributed under the terms of the Oxford University Press, Standard Journals Publication Model (https://academic.oup.com/pages/standard-publication-reuse-rights)
Keywords: autoimmunity, acute coronary syndrome, myocarditis, pericardial disease, pulmonary hypertension, right ventricular failure

Abbreviations:
- AV: atrioventricular
- CMR: cardiac magnetic resonance
- CS: Cardiac sarcoidosis
- CV: cardiovascular
- ED: Emergency Department
- EGPA: eosinophilic granulomatosis with polyangiitis
- EMB: endomyocardial biopsy
- GCM: giant cell myocarditis
- ICU: Intensive Care Unit
- IMID: Immune-mediated systemic inflammatory diseases
- mPAP: mean pulmonary arterial pressure
- PCWP: pulmonary capillary wedge pressure
- PAH: pulmonary arterial hypertension
- PH: pulmonary hypertension
- SLE: systemic lupus erythematosus
- SSc: systemic sclerosis

INTRODUCTION
Imune-mediated systemic inflammatory diseases (IMID) are a heterogeneous group of immune-mediated disorders frequently involving adverse cardiovascular (CV) manifestations. Patients with IMIDs can present with an acute cardiac condition that can be the first manifestation of the disease, such as acute myocarditis in systemic lupus erythematosus (SLE),...
or be the result of the progression of the underlying inflammatory disease, such as progressive right heart failure in systemic sclerosis (SSc). The complex pathophysiology can involve adaptive and innate immunity derangements that require careful treatment selection. In the acute setting, there must be heightened awareness by critical care specialists to improve early recognition and implementation of appropriate diagnostic and therapeutic management. In this review, we employ clinical vignettes to highlight the most common IMIDs associated with acute CV complications. We focus on the diagnostic approach, management, and role of advanced cardiovascular imaging and thoughtful diagnostic testing.

Clinical Vignette 1:
Vignette: A 55-year-old woman is seen in the emergency room for progressive shortness of breath, peripheral edema, abdominal distension, and fatigue over the past several months. The patient had a history of SLE treated with methylprednisolone and mycophenolate motefil, and frequent premature ventricular contractions treated with radiofrequency ablation. On exam, she was hypotensive with respirophasic jugular venous distention, pitting edema, and abdominal distention. A transthoracic echocardiogram showed a thickened pericardium with trace effusion and signs of interventricular dependence at Doppler analysis (Figure 1). A cardiac magnetic resonance (CMR) study showed mild thickening of the pericardium adjacent to the right ventricle, measuring up to 2.5-3 mm, and mild septal flattening and bouncing in diastole. Marked pericardial calcifications were noted. The patient was started on diuretics and referred to cardiothoracic surgery for evaluation for radical pericardiectomy.

Pericardial Disease

The approach to patients with IMIDs presenting with acute or progressive shortness of breath requires a broad differential diagnosis. Patients with SLE have a significantly increased risk of CV complications involving all structures in the heart and vasculature. Pericarditis and pericardial effusion is the most common CV presentation of SLE. The presentation ranges from paucisymptomatic to life-threatening. SLE affects pre-menopausal women more commonly than men. It is not uncommon for SLE to present in pregnant women as a flare of pre-existing or new diagnoses. Immediately recognizing the life-threatening CV conditions and their association with SLE is critical. Pericarditis with tamponade or constriction represent one of the acute CV complications encountered in critical care. The diagnostic approach to these conditions in patients with IMIDs does not differ from those without IMIDs and includes a rapid assessment with history, physical, ECG, laboratory testing, and early use of imaging tests, often in the
emergency department (ED), such as transthoracic echocardiography and chest computed
tomography. Laboratory testing should include both inflammatory and cardiac biomarkers, and
concomitant myocardial involvement is not uncommon in acute SLE pericarditis. Complications
of acute pericarditis include recurrent pericarditis, pericardial effusion that can lead to
tamponade, and pericardial thickening that can result in constriction. A study of the pericardial
fluid to exclude infectious and malignant causes of the effusion may be warranted.

In patients with IMIDs or symptoms, signs, and laboratory abnormalities suggestive of
IMIDs, a prompt referral to the rheumatologist is recommended as a rheumatologic diagnosis
and profiling provides rapid access to immunomodulating therapies that can treat and prevent
acute CV complications. Clinical suspicion and the specific IMID guide choice of laboratory
biomarkers and initial treatment (Table 1). Historical clues may often be informative if available
in the acute care setting (Table 2). For patients with acute pericarditis, with or without
tamponade, in the setting of SLE, corticosteroids are the mainstay of therapy.
Methylprednisolone or prednisone at 0.5-1 mg/kg is generally used for acute treatment. Steroid-
sparing treatments aimed at T- or B-cell responses are often added to allow for tapering of the
steroids. A higher dose of methylprednisolone is used for cases in which myocardial
inflammation is suspected and considered responsible for cardiogenic shock and/or life-
threatening arrhythmias. This approach applies to other SIDs presenting with acute pericarditis
and tamponade. Colchicine and interleukin-1 blockers (anakinra or rilonacept) have a
therapeutic role for patients in whom a diagnosis of IMIDs is not established and are diagnosed
with idiopathic, post-viral or post-procedural pericarditis or those who are refractory to other
therapies. Patients with acute pericarditis associated with IMIDs have a higher risk of effusive-
constrictive pericarditis and persistence of interventricular dependence after pericardiocentesis.
A trial of initiation or intensification of anti-inflammatory treatment is indicated for patients with
constrictive pericarditis that show signs of local and/or systemic inflammation. Diuretics and
beta-adrenergic blockers are used for symptomatic relief of right-sided heart failure. Constrictive
pericarditis not responding to medical therapy should be evaluated for radical pericardectomy
by an experienced surgical team.

CV imaging is central to the acute and subacute management of patients with acute
pericarditis, pericardial effusion, and constrictive pericarditis. Rapidly available techniques, like
echocardiography and computed tomography, are generally used acutely. Doppler
echocardiography can visualize the effusion, evaluate the hemodynamic compromise and
assess for concomitant myocardial and valvular involvement. While chest computed
tomography is not the preferred test, it can provide indirect signs of pericardial effusion and
tamponade, like a large circumferential effusion, enlargement of the inferior vena cava, and reflux of the contrast in the hepatic veins. Doppler echocardiography is also essential to identify signs of constriction when the effusion is minimal or after pericardiocentesis. When the patient is stable, CMR provides an excellent anatomic definition of the pericardium, allowing thickening, adhesions, constriction detection, and other less common findings like pericardial or myocardial masses.

Clinical Vignette 2.
A 52-year-old Caucasian man with a recent history of second-degree heart block treated with a dual-chamber pacemaker presents to the emergency room with progressive dyspnea and presyncope over two weeks. On arrival, bedside ultrasound revealed a newly depressed LVEF, and shortly thereafter, he developed sustained ventricular tachycardia requiring multiple defibrillations. Following stabilization with intravenous amiodarone, cardiac MRI revealed LVEF 21%, myocardial edema by T2-weighted imaging, and a large amount of transmural mid-wall and sub-epicardial late gadolinium enhancement in both ventricles. Endomyocardial biopsy (EMB) reveals non-caseating granulomatous inflammation (Figure 2) consistent with cardiac sarcoidosis. A chest CT demonstrated increased mediastinal lymphadenopathy and no other extracardiac features of sarcoidosis. Despite inotropic support and intravenous corticosteroids, he developed progressive cardiogenic shock requiring an intra-aortic balloon pump and expedited cardiac transplantation.

Inflammatory cardiomyopathy
Inflammatory cardiomyopathies, characterized by inflammatory cell infiltration into the myocardium with electrical instability, are commonly encountered in the intensive care unit (ICU) and require a prompt diagnosis to guide treatment. Clinical presentations include high-grade atrioventricular block, ventricular arrhythmias, resuscitated cardiac arrest, and heart failure. Patients with symptomatic high-grade atrioventricular (AV) block should receive an evaluation for coronary ischemia and Lyme carditis in endemic areas. Although the urgency of pacemaker implantation in advanced AV block often precludes more extensive evaluation, secondary testing should be pursued in patients <60 years old and those with depressed LVEF. Additional evaluation should include CMR to assess for features of inflammation, genetic testing if there is a family history of sudden death or heart block and a chest CT to screen for lymphadenopathy and pulmonary infiltrates suggestive of sarcoidosis—a systemic disease of granulomatous inflammation of uncertain etiology.
Prompt diagnosis of cardiac involvement in the setting of systemic sarcoidosis, or isolated cardiac sarcoidosis with advanced AV conduction system disease, warrants implantation of a combined pacemaker-defibrillator to prevent sudden death and anti-inflammatory therapy. When undiagnosed and untreated, cardiac sarcoidosis causes inflammatory injury and replacement fibrosis leading to progressive LV dysfunction and potent arrhythmogenic substrate. A diagnosis of CS should be considered in those with aborted sudden death, unexplained heart block, ventricular tachycardia, or new heart failure with or without established systemic sarcoidosis. Tissue diagnosis remains the gold standard for cardiac sarcoidosis. Still, the sensitivity of EMB is poor due to patchy involvement and sparing of the subendocardial tissue. Contemporary diagnostic frameworks rely on concordant findings on contrast CMR and FDG-PET/CT and the identification of extracardiac granulomatous inflammation. Isolated CS is a rare entity (<25% of cardiac sarcoidosis) but should be considered in patients with acute or chronic cardiomyopathy and electrical instability, mainly when characteristic findings on advanced cardiac imaging are present.

There is considerable clinical overlap between cardiac sarcoidosis and giant cell myocarditis (GCM), an inflammatory disorder characterized by an acute, often fulminant, clinical presentation marked by acute heart failure, multi-level conduction disease, and ventricular arrhythmias. In contrast to cardiac sarcoidosis, the yield of EMB in GCM is >80% and should be pursued when there is any clinical suspicion of GCM. Consensus recommendations on EMB support its use in patients with acute or chronic cardiomyopathy with electrical instability to rule out high-risk forms of myocarditis. Following the diagnosis of GCM, aggressive immunosuppression should be initiated, including corticosteroids and T-cell targeted therapies. When GCM or cardiac sarcoidosis presents with extensive ventricular involvement and reduced ejection fraction, salvage therapy with immunosuppression is often unsuccessful, and cardiac replacement therapy is indicated. Heart transplantation has been used successfully for both GCM and CS; however, the recurrence of inflammatory allograft disease has been described.

**Clinical Vignette 3.** A 70-year-old female presented with a 3-months history of worsening dyspnoea. On admission, she was hypoxic with signs of right heart failure and typical stigmata of SSc. Blood tests showed NTproBNP 2600, ANA +ve (anti-centromere). An electrocardiogram showed sinus rhythm with paroxysmal AF, right heart strain, and right axis deviation. Echocardiography demonstrated impaired RV function, estimated PASP of 70 mmHg, and a D-shaped LV with preserved LV function. CTPA excluded pulmonary-embolic and infiltrative lung disease (Figure 3). The patient was treated with the pulmonary vasodilators...
Sildenafil, ambrisentan, and subsequent addition of selexipa. On recovery, CMR confirmed
dilated RV with impaired function (RVEF 30%), ventricular interdependence, and normal LV
function (LV EF 57%). Invasive hemodynamics demonstrated RA 4 mmHg, mPAP 51 (94/26)
mmHg, and PCWP 2 mmHg, confirming a diagnosis of pulmonary arterial hypertension.

Pulmonary Hypertension and Right Heart Failure

Systemic sclerosis (SSc) is a systemic autoimmune condition characterized by
inflammation, microvasculopathy, and tissue fibrosis. Cardiovascular system involvement is
common and among the most frequent causes of death in patients with SSc, with the highest
prevalence in male patients and those with positive auto-antibodies and diffuse cutaneous
disease. Cardiovascular involvement in SSc occurs either as a direct result of the disease
process (primary heart involvement) or secondary to changes in other organs, particularly the
pulmonary and renal systems. A major cause of secondary heart involvement in SSc is
pulmonary arterial hypertension (PAH) due to fibro-proliferation in the pulmonary vasculature,
which affects up to 12% of patients with SSc. SSc-PAH has a worse prognosis than PAH from
other causes, with a mean survival of three years. The acute cardiovascular presentations in
patients with SSc include arrhythmias, myocarditis/pericarditis, and heart failure. Acute right
heart failure (ARHF) in patients with known SSc-PAH can be triggered by concomitant infection,
arrhythmia, or non-adherence to medical therapy but can occasionally be the first SSc disease
manifestation.

Patients with ARHF may present as a medical emergency with symptoms of progressive
shortness of breath, diaphoresis, cyanosis, cool extremities, and tachycardia. Findings on
clinical examination include systemic hypoperfusion and hypotension, signs of PAH (including
increased jugular venous pressure, a loud pulmonary component of the second heart sound and
right ventricular heave), and a pansystolic murmur of tricuspid regurgitation. Signs of chronic
RHF (hepatomegaly, ascites, and peripheral edema) may be present, but ARHF may not be a
prominent feature. First-line diagnostic tests should include standard biomarkers (NT-proBNP,
infection, and inflammatory markers), an electrocardiogram, a chest CT to detect pulmonary and
cardiovascular pathology, and a transthoracic echocardiogram. The clinical picture and
management of ARHF in SSc patients is often more complex than in patients without SSc and
can be caused by a combination of factors, including infiltrative lung disease, pulmonary venous
occlusive disease, and left heart failure from primary heart involvement.

Cardiovascular imaging is essential for diagnosing heart involvement and managing
ARHF in patients with known or suspected SSc. 2D echocardiography will typically be the first-
line imaging test and can assess left and right-sided chamber size and function, exclude other
causes of heart failure such as valve disease and estimate pulmonary arterial systolic
pressure\textsuperscript{23}. A tricuspid regurgitation jet velocity greater than 3.4 m/s by echocardiography
generally indicates PH \textsuperscript{23}. RV and RA dilation, septal deformity, and a short right ventricular
ejection acceleration time suggest underlying chronic PH. Multidetector CT should be
considered as early as possible to provide volumetric information about RV size and function
and detect signs of interstitial lung disease. In convalescent patients, CMR allows the most
accurate assessment of RV size and function and detection of primary (left) heart involvement in
SSc using late gadolinium enhancement, detecting subclinical disease in more than half of SSc
patients\textsuperscript{24}. Ultimately, right heart catheterization is the reference test to diagnose PHT, with
mean pulmonary artery pressure (mPAP) of ≥25 mmHg at rest with a mean PCWP of <15
mmHg and PV resistance of more than 3 Woods Units considered diagnostic \textsuperscript{23}.

The management of ARHF in SSc is a complex medical emergency with poor outcomes,
and early involvement of PH and rheumatology experts is essential to deliver optimal care.
Admission to an intensive care environment is usually required to allow optimal hemodynamic
monitoring and fluid management. The treatment of ARHF is set out in international practice
guidelines and includes optimization of RV volume and preload, RV afterload with
pharmacotherapy, and if needed, mechanical circulatory support and treatment to support
myocardial contractility\textsuperscript{24}. Therapies specific to SSc and PHT may be added early in
consultation with the multidisciplinary team, including prostacyclin analogs, phosphodiesterase
inhibitors, and endothelin receptor antagonists.

\textbf{Clinical Vignette 4.} A 26-year-old female of Asian descent presented to the emergency room
with shortness of breath. She was tachypneic and hypoxic (SpO\textsubscript{2} 90\%), with a heart rate of 105
bpm, right arm blood pressure of 60/40 mmHg, and 120/50 mmHg in the left arm. She had
elevated jugular venous pressure, pulmonary crackles, a soft midsternal diastolic murmur, and a
diminished right radial pulse. A whole body computed tomography scan displayed diffuse soft
tissue wall thickening in the ascending to descending aorta, right subclavian artery stenosis, and
a 5.5cm dilated aortic root with severe aortic insufficiency noted on echocardiography (\textbf{Figure
4}). The ESR and CRP were both elevated, and Takayasu arteritis was diagnosed. She required
diuresis and high-dose steroids and was eventually stabilized on methotrexate and an IL-6
inhibitor and underwent successful bioprosthetic aortic valve with aortic root replacement.

\textbf{Systemic Vasculitis and Acute Vascular Syndromes:}
The 2012 Chapel Hill Consensus Conferences characterizes vasculitis into large, medium, and small vessel vasculitis (although considerable overlap can occur) along with others such as variable vessel, single organ vasculitis, and those associated with systemic diseases and probable etiologies (Table 2).\textsuperscript{25,26} Vasculitis is rare. For example, a more common large vessel vasculitis, giant cell arteritis, even in the most enriched population, has an incidence of 22 per 100,000.\textsuperscript{26} Thus, diagnosing vasculitis with its associated vascular, valvular, pericardial/myocardial, or coronary complications in the acute cardiovascular setting requires a high index of suspicion.

In those with acute coronary syndromes, vascular pathologies, and/or multiple venous or arterial occlusive events or stenotic lesions, age, sex, and race/ethnicity help direct assessment. For example, giant cell arteritis generally presents after 50 years of age, while Takayasu arteritis is younger (< 40) and predominantly female.\textsuperscript{27} An ischemic cerebrovascular or myocardial infarction in a young individual (< 45 years of age) should include large or medium vessel (e.g., polyarteritis nodosa) vasculitis on the differential. Serologic assessment with inflammatory biomarkers is essential, but relatively non-specific (e.g., ESR/CRP elevation, and most helpful in vasculitis associated with systemic diseases, those of probable etiology, or the ANCA and IgG4-related vasculitis, and in ruling out infection (Table 2).

A key component of large vessel vasculitis assessment includes multimodality imaging allowing diagnostic, prognostic, and management implications. In acute cardiovascular care, this frequently consists of a whole-body computed tomography scanning (given availability, speed, and ease) with intravenous IV contrast and echocardiography. Invasive coronary angiography rules out plaque rupture and dissection and can diagnose characteristic coronary vasculitis complications (such as ostial lesions in Takayasu arteritis, beaded pattern in polyarteritis nodosa, and aneurysmal in Kawasaki). MRI/MRA is helpful for cerebrovascular events when computed tomography is contraindicated and utilized in combination with vascular FDG-PET to assess response to therapy and monitor over time.

The acute management of vasculitis typically includes immunosuppression, most often corticosteroids, after ruling out infectious etiology. In the critical care setting, problems with venous and arterial access/hemodynamic monitoring and maintaining perfusion pressure issues in critical vertebral and carotid stenosis can arise. A multi-disciplinary approach involving rheumatology is always necessary, especially given the nuances of specific vasculitis conditions. For example, in Bechet’s disease, venous and arterial embolisms are treated with immunosuppression, as anti-coagulants and anti-platelets are often contra-indicated. In eosinophilic granulomatosis with polyangiitis (EGPA), cardiovascular involvement
(pericardial/myocardial, arrhythmias including ventricular tachycardia) accounts for 50% of EGPA-related deaths and strongly influences aggressiveness of treatment (e.g., cyclophosphamide-based therapy). Finally, surgical interventions, if required, are preferred when disease activity is quiescent to minimize suturing into friable tissue, limit issues related to pathergy, and allow for enhanced wound healing.

**Acute Multidisciplinary Approach**

Beyond prompt recognition, individualized guideline-based management with a multidisciplinary team-based approach should be incorporated to improve prognosis. As the provider who primarily manages the care of the acutely ill patient, the acute CV care specialist (often a general cardiologist or cardiac intensivist) plays a critical role in this team-based approach, frequently representing the “front-line" or initial care provider. Although intravenous steroids are often utilized in the acute CV setting when aggressive and rapid anti-inflammatory therapy is needed, high-dose steroids may have unwanted side effects, and certain conditions may be less responsive than others or have a more targeted immunotherapy approach. As such, they must be familiar with the spectrum of IMIDs and associated cardiovascular complications to recognize these clinical scenarios. Careful collection of a thorough history and physical can be invaluable in identifying an acute inflammatory condition (e.g., note of extracardiac manifestations of IMIDs). The standard diagnostic evaluation should always be performed, such as evaluation for evidence of acute myocardial injury, inflammation, or infection, ruling out other causes of unstable arrhythmias (e.g., Lyme disease or ACS), and assessing myocardial function, as appropriate, based on the presentation. Upon recognizing a possible or probable acute CV complication of IMID, the acute CV care specialist should ensure appropriate immediate (and anticipatory) triage and stabilization. For example, in a patient presenting with fulminant myocarditis, the provider should consider the possibility of decompensation due to progressive electrical or hemodynamic instability and plan accordingly (e.g., consider options for temporary mechanical support).

In parallel with the initial evaluation and triage, the acute CV care specialist should engage subspecialty consultative services, such as rheumatology, cardio-rheumatology, pulmonary vascular, advanced heart failure, and cardiovascular imaging (Central Illustration). The subspecialists can then weigh in on additional non-invasive diagnostic evaluations, including serologic testing or imaging, and on the role of invasive diagnostics (e.g., biopsy). The subspecialists can guide empiric therapy while diagnostic evaluations are ongoing (e.g., empiric steroids) and also on specifically tailored treatment once a diagnosis is established.
Furthermore, the subspecialists can educate the team on the natural history of the disease, the likelihood and time course for response to interventions, and any other potential downstream complications associated with the disease process.

Finally, as the primary provider for the patient, the acute CV care specialist should facilitate multidisciplinary team-based discussions, if able, to streamline communication and expedite the workup and management. In collaboration with their subspecialty colleagues, the acute CV care provider should synthesize the multidisciplinary team recommendations, facilitate the treatment plan and provide the patient and family support and education in the acute setting.

**SUMMARY AND CONCLUSIONS**

Patients with IMIDs are at an increased risk of acute CV disease, and rapid recognition through multidisciplinary collaboration from critical care specialists, cardiology, and rheumatology is integral to preventing adverse clinical outcomes. Cardiovascular multimodality imaging is essential in evaluating and managing, as highlighted in this review (Central illustration). The armamentarium of immunotherapies continues to evolve rapidly, and this growing unmet need highlights the importance of the need for future development of the field of cardio-rheumatology.

**Table 1. Acute CV Manifestations of IMIDs: Clinical Biomarkers and Immunosuppression**

<table>
<thead>
<tr>
<th>Cardiovascular Manifestation</th>
<th>Laboratory Markers</th>
<th>Medications/Immunosuppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pericardial Disease</td>
<td>hs-CRP, ESR, CBC with differential*&lt;br&gt;Disease-specific autoantibodies: <strong>• SLE: ANA^, Smith, Ro/La (SSA/SSB), dsDNA, antiphospholipid antibodies^</strong>&lt;br&gt;<strong>• RA: RF, anti-CCP</strong>&lt;br&gt;<strong>• MCTD/SSc: U1RNP, Scl-70, RNA polymerase III, Centromere antibodies or ANA in centromere pattern</strong>&lt;br&gt;<strong>• EGPA: ANCA, myeloperoxidase, and proteinase 3 antibodies</strong></td>
<td>First-line: high dose NSAIDs, colchicine 0.6 mg BID&lt;br&gt;<strong>• If refractory/recurrent and failed first line: prednisone 0.2-0.5 mg/kg/day with a slow taper, IL-1 inhibition: anakinra 100 mg daily, rilonacept 320 mg loading x1, then 160 mg weekly.</strong>&lt;br&gt;<strong>Autoimmune Disease-specific:</strong>&lt;br&gt;<strong>• methylprednisolone or prednisone 0.5-1mg/kg, or pulse dose IV steroid for concomitant myocardial involvement or severe cases.</strong>&lt;br&gt;**• Steroid sparing options: Azathioprine: start at 50 mg titrate to 1-2mg/kg daily, MMF: 500 mg PO BID titrate to 1-1.5 g PO BID, IVIG: 2g/kg over 3-5 days^2^&lt;br&gt;<strong>Caution for the use of steroids in SSc with pericarditis</strong></td>
</tr>
<tr>
<td>Inflammatory Cardiomyopathy</td>
<td>hsTnT, NT-proBNP, hsCRP, ESR, CBC with differential Cardiac sarcoidosis: ACE level can be considered, but low</td>
<td>Cardiac sarcoid: prednisone 0.5-1mg/kg MTX 5-15mg PO/weekly, or MMF dosing as above. Anti-TNF therapy (infliximab or adalimumab) is used for refractory disease or as steroid-sparing</td>
</tr>
</tbody>
</table>
| Systemic Sclerosis (Scleroderma) | Autoantibodies: RNA polymerase III, Centromere antibodies, or ANA in centromere pattern | Immunosuppression guided by organ manifestations includes MTX, MMF, AZA, and cyclosporine. Steroids are avoided, given the increased risk of precipitating scleroderma renal crisis. **SSc Subtype:**  
- SSc-active Raynaud’s, microvascular coronary disease: Amlodipine, Nifedipine + long-acting nitrates, Sildenafil  
- SSc-acute myocarditis: immunosuppressants + steroids  
- Group 1 SSc-PAH: upfront combination therapy (PDE5 + ERA)  
- Group 2 SSc-PVH: preliminary data for SGLT-2 and MRA in SSc-HfPEF, SSc-HfReEF without inflammation, standard GDMT  
- Group 3 SSc-ILD-PH: standard immunosuppressant therapy (MMF or cyclophosphamide) + biological and antifibrotic therapies |
| --- | --- | --- |
| Vasculitis | hs-CRP, ESR, CBC with differential* % Disease-specific antibodies as above plus immune complex; IgA, anti-GBM, IgG4, HLA B51 (Bechet’s), cryoglobulins, complement, RF, hepatitis serologies | General management for most vasculitides includes medium to high-dose corticosteroids as induction therapy with the addition of DMARD/biologic for maintenance as guided by the disease. **Disease-specific treatments:**  
- ANCA-associated vasculitis: induction with steroids, cyclophosphamide (15mg/kg), and rituximab with maintenance regimens defined by subtype.  
- Kawasaki: IVIG 2g/kg over 3-5 days²⁶ |

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; CCP: cyclic citrullinated peptide; DMARD: drug modifying anti-rheumatic disease therapy; dsDNA: double-stranded DNA; EGPA, eosinophilic granulomatosis with polyangiitis; HfPEF: heart failure with preserved ejection fraction, ILD: interstitial lung disease MCTD: mixed connective tissue disease; GBM: glomerular basement membrane; MMF: mycophenolate mofetil; PAH: pulmonary arterial hypertension; PVH: pulmonary venous hypertension, RA: rheumatoid arthritis RF: rheumatoid factor: SLE: systemic lupus erythematosus; SSc: systemic sclerosis,  

*Assess for leukopenia, anemia, thrombocytopenia, and eosinophilia. ANA: anti-nuclear antibody. *Titer ≥ 1:80 is considered positive and can be seen in CTD; SSc patients can develop PH across WSPH Group 1-3 classifications.³¹
### Table 2: Clinical clues of IMIDs

<table>
<thead>
<tr>
<th>Rheumatologic Disease</th>
<th>Clinical Clues</th>
</tr>
</thead>
</table>
| **Systemic Lupus Erythematosus** | • Malar Rash  
• History of rash, especially sun-exposed areas  
• Weight loss (especially active disease)  
• Serositis  
• Raynaud’s  
• Lymphadenopathy  
• Oral Ulceration  
• Alopecia |
| **Connective Tissues Diseases** | • Sclerodactyly - below vs. above elbows, limited vs. diffuse  
• Microstomia  
• Signs of pulmonary HTN  
• Interstitial lung disease |
| **Inflammatory Arthritis** | • Joint pain and swelling in classical distributions.  
• Psoriatic skin manifestations with PsA  
• PsA: nail findings (including pitting) |
| **Sarcoidosis** | • RBBB or atroventricular block  
• Pulmonary disease  
• Skin disease (such as lupus pemio)  
• Uveitis |
| **Vasculitis** | • AAV: varies with subtype and includes: rashes, sinusitis, epistaxis, hemoptysis, cough, nasal bridge collapse, ocular inflammation, joint pain  
• Bechet’s - orogenital ulceration, ocular inflammation, pathergy  
• GCA - temporal headache, scalp tenderness, jaw claudication, polymyalgia symptoms (shoulder and pelvic girdle stiffness and weakness) systemic symptoms, especially fevers, weight loss, night sweats.  
• Takayasu - absent peripheral pulses - classically upper limb but can be a lower limb, discordant BP, classical imaging features of the arterial tree, systemic symptoms, especially fever and night sweats |

Abbreviations: PsA: psoriatic arthritis, RBBB: right bundle branch block. AAV: ANCA-associated vasculitis

*Inflammatory arthritis: Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis.

### Table 3: Cardiomyopathies presenting with Electrical Instability

<table>
<thead>
<tr>
<th>Category</th>
<th>Cardiomyopathy</th>
</tr>
</thead>
</table>
| **Inflammatory** | Cardiac sarcoidosis (granulomatous myocarditis)  
Giant cell myocarditis  
Immune checkpoint inhibitor myocarditis  
Lymphocytic myocarditis  
Eosinophilic myocarditis |
| **Genetic** | Arrhythmogenic cardiomyopathy  
Lamin A/C cardiomyopathy  
Noncompaction cardiomyopathy  
End-stage hypertrophic cardiomyopathy |
| **Infectious** | Chagas disease *(Trypanosoma cruzi)*  
Lyme carditis *(Borreli burgdorferi)* |
| **Metabolic** | Cardiac iron overload, including hereditary hemochromatosis |
| **Infiltrative** | Amyloid  
Glycogen storage disease (i.e., Fabry’s)  
Hydroxychloroquine mediated cardiomyopathy |
### Table IV: Overview of Vasculitides with Acute CV Complications

<table>
<thead>
<tr>
<th>Vasculitides Associated with Systemic Disease</th>
<th>Specific Disease</th>
<th>Vascular complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic Lupus Erythematosus</td>
<td></td>
<td>Pancarditis, valve disease, accelerated atherosclerosis, thrombosis, small to medium vessel vasculitis</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td></td>
<td>Pancarditis, vasculitis similar to PAN, accelerated atherosclerosis</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td></td>
<td>Vascular granulomatous infiltration</td>
</tr>
<tr>
<td>Inflammatory Bowel Disease (Crohn's disease)</td>
<td></td>
<td>Associated with TAK</td>
</tr>
</tbody>
</table>
| IgA-related disease                          |                  | Abdominal aortic aneurysm/
|                                              |                  | peri-aortitis/coronary aneurysm |
| Ankylosing Spondylitis, Reactive arthritis   |                  | Aortic insufficiency (w/ aortic root dilatation), aortitis (ascending thoracic aneurysm) |
| Antiphospholipid syndrome                    |                  | Valvular regurgitation, systemic thrombosis including cerebrovascular and coronary events/myocarditis/ dilated cardiomyopathy secondary to thrombotic microangiopathy |
| Relapsing polychondritis                     |                  | Aortic insufficiency |
| Vasculitides Associated with Probable Etiology |                  | Rare cardiovascular complications including myocardial involvement |
| Viral Induced                                |                  | Rare cardiovascular complications including myocardial involvement |
| Hepatitis C – associated cryoglobulinemic vasculitis, Hepatitis B polyarteritis nodosa associated vasculitis, SARS-CoV-2 vasculitis |                  | Aortitis (at sites of pre-existing injury/atherosclerosis), Ascending and thoracic aorta involvement (syphilis) |
| Bacterial                                    |                  | Aortitis (at sites of pre-existing injury/atherosclerosis), Ascending and thoracic aorta involvement (syphilis) |
| Drug Induced                                 |                  | Large to small vessel vasculitis (e.g. drug induced ANCA Vasculitis) |
Figure 1: 55-year-old female with long-standing SLE presenting with acute shortness of breath. A. Parasternal 2D echocardiographic long-axis image shows increased echogenicity and thickening of the anterior pericardium. B. LV global longitudinal strain demonstrates reduced strain of the basal anterior and lateral wall segments, a pattern seen in constrictive pericarditis. C. Systolic flow reversal is noted in the hepatic vein Doppler signal consistent with elevated right ventricular end-diastolic pressure. D. Transaxial 4-chamber image and E. transaxial longitudinal view demonstrated dense calcification and thickening of the anterior pericardium extending to the left ventricular apex. Paradoxical septal motion is noted from the short-axis CMR images in systole (F) and diastole (G), suggestive of interventricular dependency and constrictive physiology.

Figure 2. Acute heart failure in cardiac sarcoidosis. A.) Cardiac magnetic resonance imaging: 3-chamber view demonstrating dense, transmural late gadolinium enhancement (white arrowheads) in the left ventricle and septum. (B. Photomicrograph showing a large non-necrotizing granuloma with associated lymphocytic inflammation (blue arrowheads) within the explanted myocardium adjacent to epicardial adipose tissue. H&E stained section, 100x original magnification. Photomicrograph courtesy of Robert F. Padera MD Ph.D., Brigham and Women’s Hospital, Boston, MA.

Figure 3. Pulmonary hypertension and RHF in SSc. Pulmonary hypertension and RHF in SSc. A. Apical 4-chamber echocardiogram demonstrates severe right atrial and ventricular enlargement with moderate-severe tricuspid regurgitation. B. Continuous wave Doppler across the tricuspid jet demonstrates RVSP 76 mmHg, which is consistent with severe pulmonary hypertension when added to the right atrial pressure. Cardiac magnetic resonance image in systole (C) and diastole (D) dilated right ventricle with flattening of the interventricular septum and impaired function (RVEF 30%).

Figure 4: 28 y/o female presenting with shortness of breath and asymmetric radial pulses. A. Computed tomography angiogram with coronal imaging at the level of the aortic arch demonstrating significant vessel thickening. B. Computed tomography angiogram with coronal and C sagittal MIP reconstructions displaying significant bilateral common carotid artery thickening with concomitant narrowing.
Figure 5: Central Illustration. Conceptual model of the role of multidisciplinary care in patients with IMIDs who require ICU-level care. *If available, consider cardio-rheumatology consultation.

** For pulmonary hypertension management, consider pulmonary vascular specialists as available. ^Advanced heart failure involvement for mechanical support and/or heart transplant evaluation.

References


*Figure 1*

165x76 mm (x DPI)
Figure 2
165x72 mm (x DPI)
Figure 3
146x141 mm (x DPI)
Acute IMIDs requiring ICU care

**Graphical Abstract**

165x124 mm (x DPI)