

MYOCARDITIS RESOURCE/DOT PHRASE

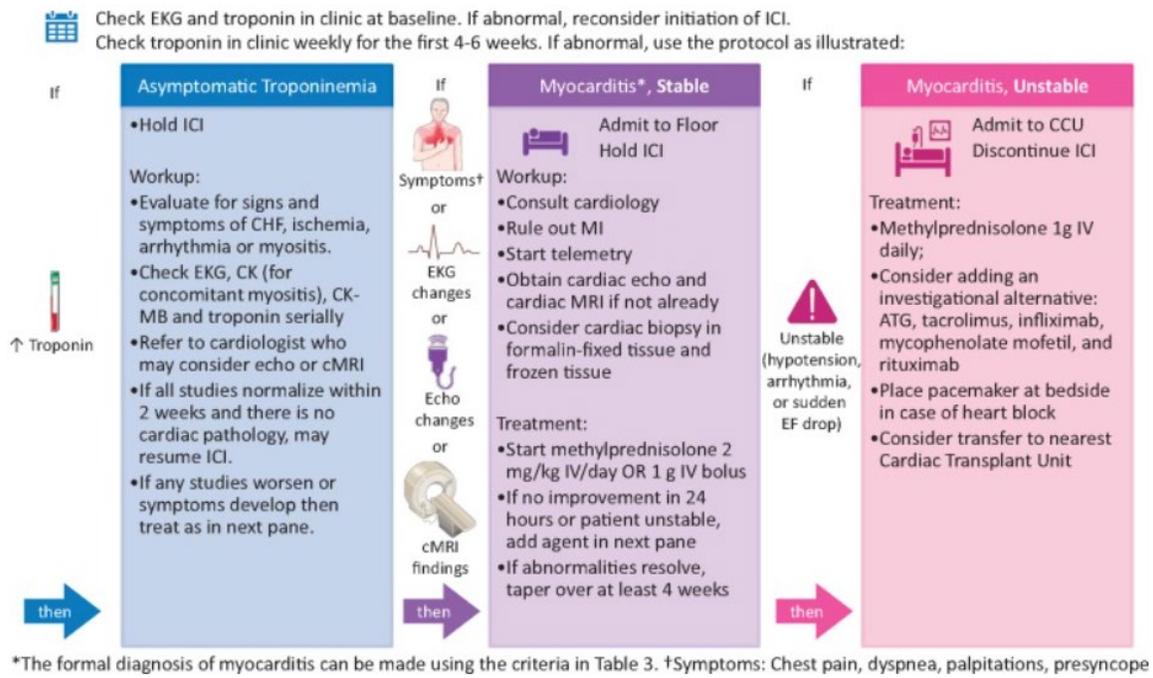
Please start a secure email or messaging chain for the patient including the cardio-oncologist, cardiology consult team, and oncology consult team, if there is no inpatient cardio-oncology consult team.

Thank you for your care of our cardio-oncology patients in the hospital on the cardiology consults service. As you may be aware, there have been more frequent cases of myocarditis induced by immune checkpoint inhibitors (ICIs; antagonists of CTLA-4, PD-1, or PDL-1, which are receptors on the T cell), especially in the pandemic. It is unclear whether there is any relationship with COVID-19 itself or the vaccine, in the setting of cancer care.

MONITORING FOR POSSIBLE DEVELOPMENT OF MYOCARDITIS WITH INITIATION OF ICI THERAPY

On immune checkpoint inhibitor therapy, the patient should be monitored closely, with troponin and ECG weekly for the first 4-6 weeks on therapy if possible. If symptoms, ECG changes or new elevations in troponinemia occur on immune checkpoint inhibitor therapy, the patient should be evaluated for possible myocarditis.

MYOCARDITIS ALGORITHM FROM EARLY 2019s



<https://europepmc.org/article/PMC/6452314>

NEW PREFERRED SECOND AGENT SINCE LATE 2019: ABATACEPT

Abatacept is a CTLA-4 agonist typically used for rheumatoid arthritis. Abatacept has been shown in case reports since 2019 to be efficacious and life-saving in steroid-refractory myocarditis, which typically can associate with myositis and/or myasthenia gravis. Consider starting this drug if the patient is not improving 24 hours after methylprednisolone 2g mg IV bolus, or if troponin continues to rise, or if arrhythmias occur. Abatacept can be prescribed by any clinician.

The abatacept dosing is as follows. Abatacept 500 mg IV q2weeks for a total of 5 doses.

This was the dosing in the two case reports below. It is also the dose we have used for patients so far.

A. <https://casereports.bmj.com/content/14/11/e244334> B. <https://academic.oup.com/ehjcr/article/5/11/ytab342/6354360>

In addition to abatacept, CellCept should also be considered if needed.

TIMING OF MYOCARDITIS

Myocarditis as a toxic cardiovascular effect of immune checkpoint inhibitors has been seen typically within 4-6 weeks, or as late as 240 days (8 months) following therapy particularly for melanoma, and is more often seen with combination therapy (which he has received) compared to single-drug therapy.

<https://www.ncbi.nlm.nih.gov.proxy.lib.mcw.edu/pmc/articles/PMC6287923/>

LAB TESTS

Lab tests that are helpful in myocarditis: Troponin and CKMB, NT-proBNP; CKMB can help confirm myocarditis and can help determine if CK is only or also due to myocarditis. NT-proBNP can be helpful if heart failure may be present.

Troponin and all of these may be normal in myocarditis in some cases, as can the ECG; any new ECG changes, even non-specific or idiopathic ones like PVCs can be consistent with myocarditis.

CMR AND ENDOMYOCARDIAL BIOPSY

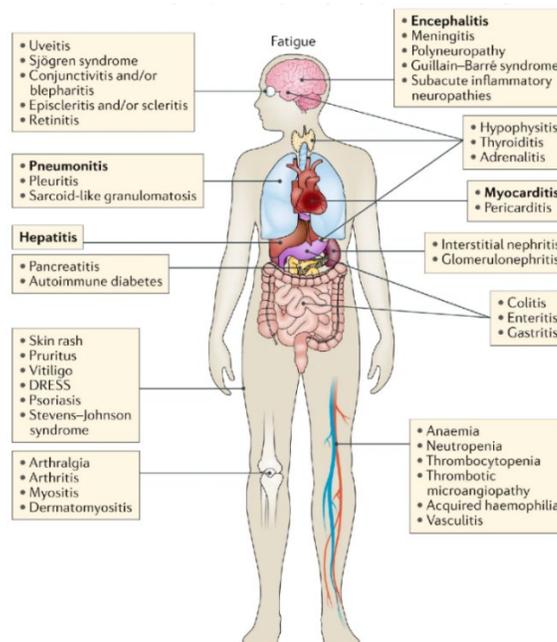
If a CMR cannot be obtained in one or two days and the patient is not improving, consider endomyocardial biopsy. Note that neither is 100% sensitive for myocarditis. **CMR** can be helpful in making the diagnosis of myocarditis if present, but CMR is not 100% sensitive, and the yield may be as low as under 40%. **Endomyocardial biopsy** is the gold standard for confirming the diagnosis of myocarditis. However, because T-cell infiltration of the myocardium is patchy, six or more biopsies from varying endomyocardial regions are anticipated for facilitating diagnosis; yet even then, a high rate of false negatives may exist.

<https://europepmc.org/article/PMC/6452314>

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7205467/>

CONSTELLATION OF INFLAMMATORY/AUTOIMMUNE MULTI-ORGAN FINDINGS

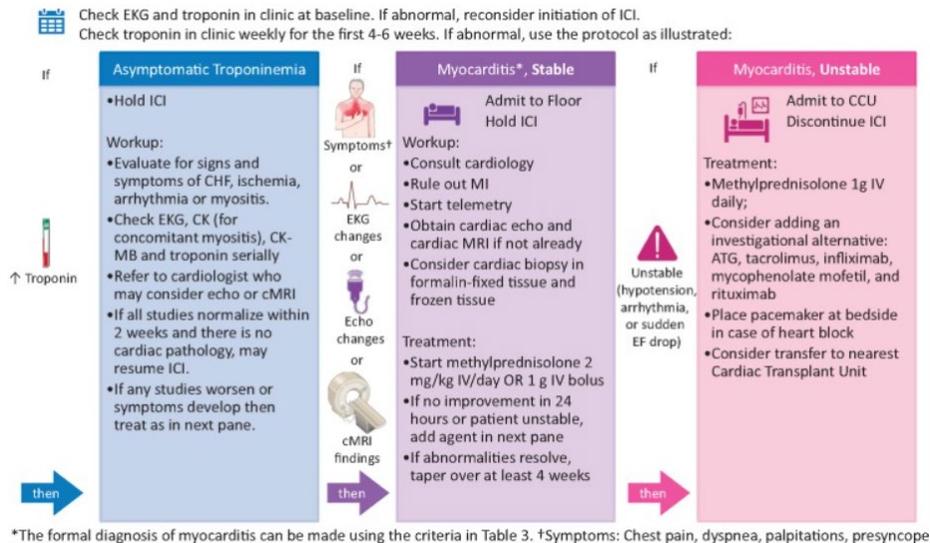
It should be recognized that a constellation of ICI adverse effects typically occurs, although rare. Myocarditis is often diagnosed after myasthenia gravis or myositis is already noted. The patient may likely have myocarditis, along with inflammation of other body organs (if evidence exists, such as new drooping eyelid suggesting myasthenia gravis, new elevated LFTs suggesting hepatitis, new abnormal thyroid function tests suggesting thyroiditis, new elevated diaphragm suggesting myositis (with elevated CK), etc).



<https://www.nature.com/articles/s41571-019-0218-0>

TREATMENT

STEROIDS: Start methylprednisolone 1 g IV bolus Q24H. This dose is typically higher than the dose used for ICI-induced hepatitis, thyroiditis, myositis, pneumonitis, or myasthenia gravis, for example. Note that all of these can associate with ICI-induced myocarditis. Typically, methylprednisolone 1 g IV bolus/day or 2 mg/kg IV/day is used to treat myocarditis due to ICI. For steroid-refractory myocarditis, a variety of alternative immunosuppressive agents can be added. On discharge, a typical steroid taper can be used.



<https://europepmc.org/article/PMC/6452314>

ABATACEPT: Most recently, case reports in the past few years have indicated great efficacy of abatacept (CTLA-4 agonist) to treat steroid-refractory myocarditis (and other associated ICI adverse effects) due to CTLA-4 or PD-1 inhibitors, such as nivolumab, ipilimumab, and pembrolizumab, among other ICIs. Abatacept has been coupled with steroid therapy, or with CellCept and steroid therapy, and so on for myocarditis (and other ICI adverse events).

SEE CASE REPORTS:

1. FIRST EVER; ICI=Nivolumab, PD-1 inhibitor.

Abatacept for Severe Immune Checkpoint Inhibitor–Associated Myocarditis

<https://www.nejm.org/doi/full/10.1056/NEJMc1901677>

2. ANOTHER EXAMPLE; (ICIs=Nivolumab+Ipilimumab, PD-1 inhibitor plus CTLA-4 inhibitor).

A case report of immune checkpoint inhibitor-related steroid-refractory myocarditis and myasthenia gravis-like myositis treated with abatacept and mycophenolate mofetil

<https://academic.oup.com/ehjcr/article/5/11/ytab342/6354360>

3. Myocarditis plus myasthenia gravis; ICI: pembrolizumab, PD-1 inhibitor.

Life-threatening immune checkpoint inhibitor-induced myocarditis and myasthenia gravis overlap syndrome treated with abatacept: a case report

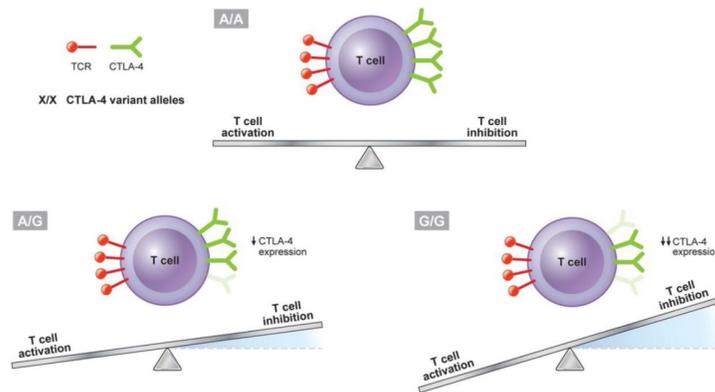
<https://casereports.bmj.com/content/14/11/e244334>

4. Immune Checkpoint Inhibitor-Associated Myocarditis With Persistent Troponin Elevation Despite Abatacept and Prolonged Immunosuppression

<https://www.jacc.org/doi/10.1016/j.jacc.2020.10.013>

This all makes sense, given that the CTLA-4 and PD-1 receptors are on the T cell, and ICIs lead to enhanced activation of the T cells, while abatacept limits activation of the T cells.

<https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.117.029626>.



<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8855704/>

MYOCARDITIS, MYASTHENIA GRAVIS, AND ARRHYTHMIA

The risk of arrhythmia may persist until troponin normalizes and myocarditis resolves. Depending on any scar from myocarditis, the patient may also be at risk of arrhythmia after resolution of myocarditis. Beta blockers may not be good to use in the setting of myasthenia gravis, but may be helpful acutely for SVT if needed. If the patient develops VT, amiodarone should be used instead of metoprolol. The cardiology on-call team should be called to determine whether to move the patient to the cardiology service or the CCU, and whether to consult EP.

SUSPECTED MYOCARDITIS NOT CONFIRMED ON PATHOLOGY OR CMR

Given that he is clinically well and his EF is stable, albeit low, it would be reasonable to continue current CV management without steroids for possible myocarditis not confirmed on pathology. If he for any reason becomes clinical unwell from a cardiopulmonary standpoint or if he EF declines further, steroids should be considered for possible myocarditis not confirmed on pathology. It would be reasonable to monitor with periodic ECGs, as well as troponin, NT-proBNP, CK, and CKMB to ensure there are no new changes that could suggest progressive myocarditis not confirmed on pathology.

ICI RECHALLENGE

If the patient must have continued immunotherapy, avoid combination immunotherapy, as in the clinical trial.

LITERATURE RESOURCES ON THE SAFETY/EFFICACY OF ICI RECHALLENGE

<https://www.sciencedirect.com/science/article/pii/S0169500219307858>

<https://pubmed.ncbi.nlm.nih.gov/32815895/>

<https://jamanetwork.com/journals/jamaoncology/fullarticle/2764543>

<https://jamanetwork.com/journals/jamaoncology/fullarticle/2766793>

<https://pubmed.ncbi.nlm.nih.gov/32469396/>

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7295425/>

<https://pubmed.ncbi.nlm.nih.gov/31461381/>

EXAMPLE RECOMMENDATIONS

IF INITIATING ICI:

1. Weekly troponin and ECG while on immune checkpoint inhibitor therapy, for the first 4-6 weeks.

IF MYOCARDITIS:

1. Methylprednisolone 1 g IV bolus Q24H.
2. Please make preparations for inpatient administration of abatacept if needed.
3. Please prepare to give CellCept also if needed.
4. If ptosis is present, please share these papers with Neurology to consider:
 - a, Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance <https://www.nature.com/articles/s41571-019-0218-0>, especially Figure 2.
 - b, Myocarditis plus myasthenia gravis; ICI: pembrolizumab, PD-1 inhibitor. Life-threatening immune checkpoint inhibitor-induced myocarditis and myasthenia gravis overlap syndrome treated with abatacept: a case report <https://casereports.bmj.com/content/14/11/e244334>
5. Cardio-Oncology Clinic consult upon hospital discharge.

Sherry-Ann Brown MD PhD, Director of Cardio-Oncology and Assistant Professor of Medicine, F&MCW