Neuromuscular irAE's & 'Triple-M Syndrome'

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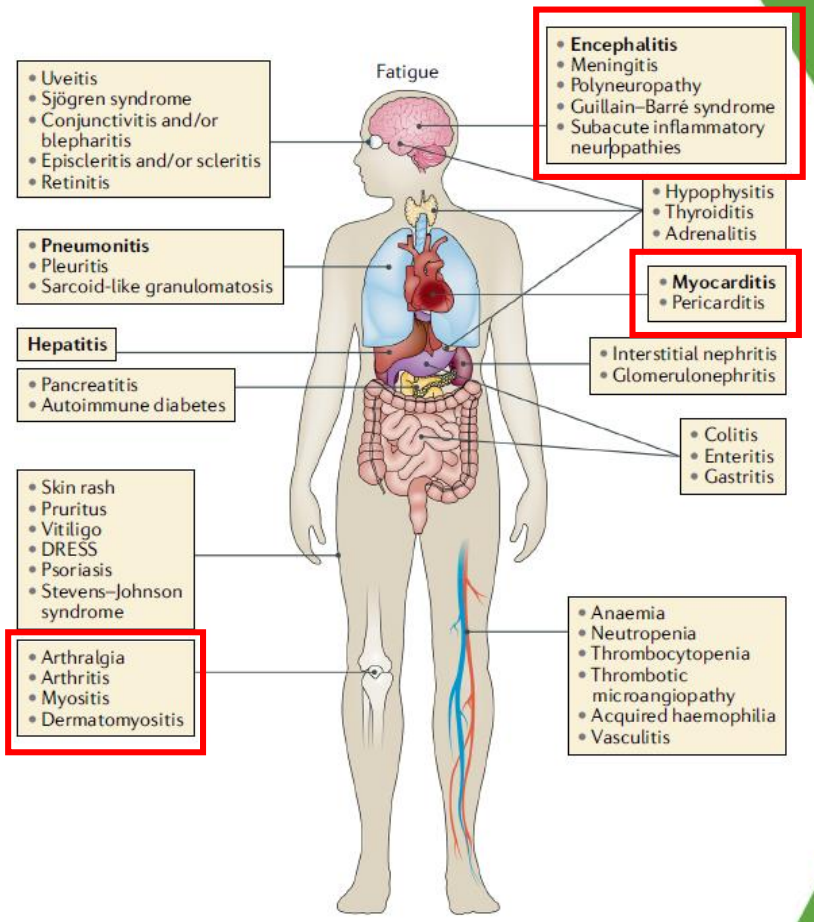
Neuromuscular irAE's

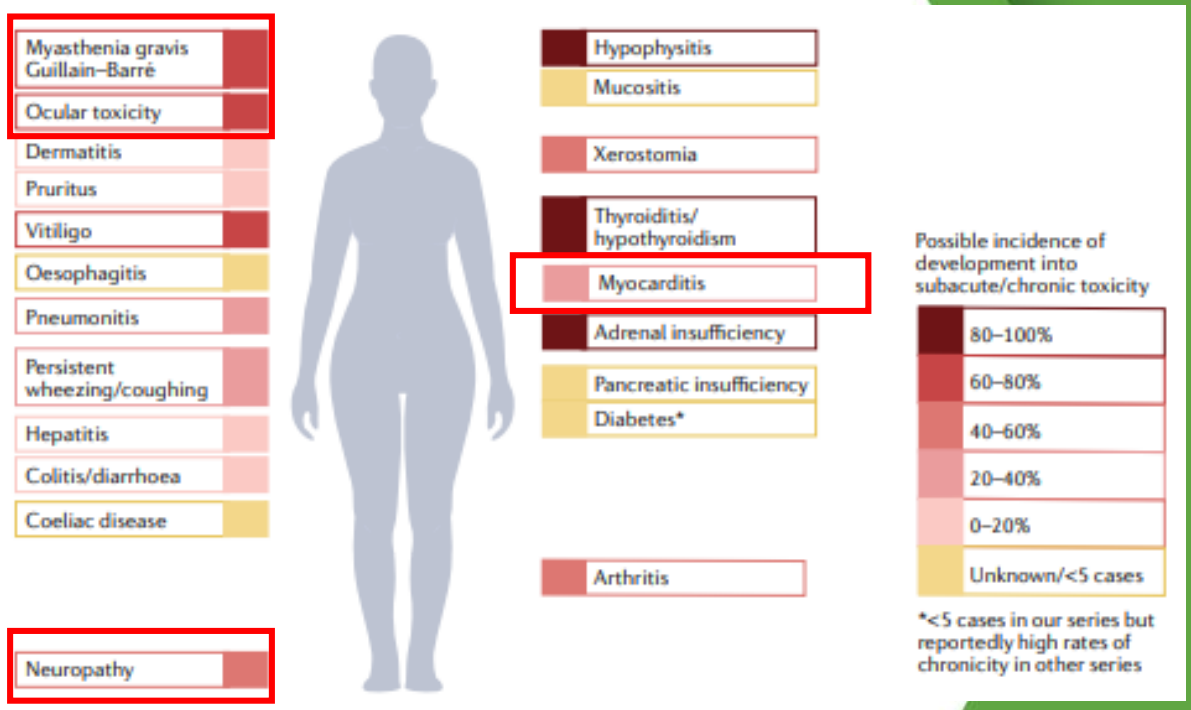
- Immune-related neuromuscular irAEs are rare, but potentially life-threatening
- Occur in 1-5% of patients
- Can occur as a syndrome encompassing multiple organs, including myocarditis
- Increased incidence with dual ICB
- Known risk factors are limited (hx of autoimmune disease)



Martins et al Nature 2019

Neuromuscular irAEs

- The burden of NMirAE's is not just immediate
- High rates of chronic manifestations, with significant impact on QOL



Johnson et al. Nature 2022

Myositis

- Overall incidence is <1% of all patients, but estimated MC neurologic irAE
- Typical onset is within 5-6 weeks
- Symptoms can be variable and progress quickly
  - Muscle pain/weakness
  - Head drop, ptosis
  - Life-threatening if respiratory/bulbar involvement
- Elevated **CK**, **EMG changes**, antibodies are often negative

Jordan et al J ESMO Open 2021
Alsalem et al Current Oncology 2023

Myasthenia Gravis

- IrAE MG frequently overlaps with myositis and other irAEs
- More fulminant than idiopathic cases, with >50% having respiratory or bulbar weakness
- Acetylcholine receptor autoantibodies can be seen, but not in all cases

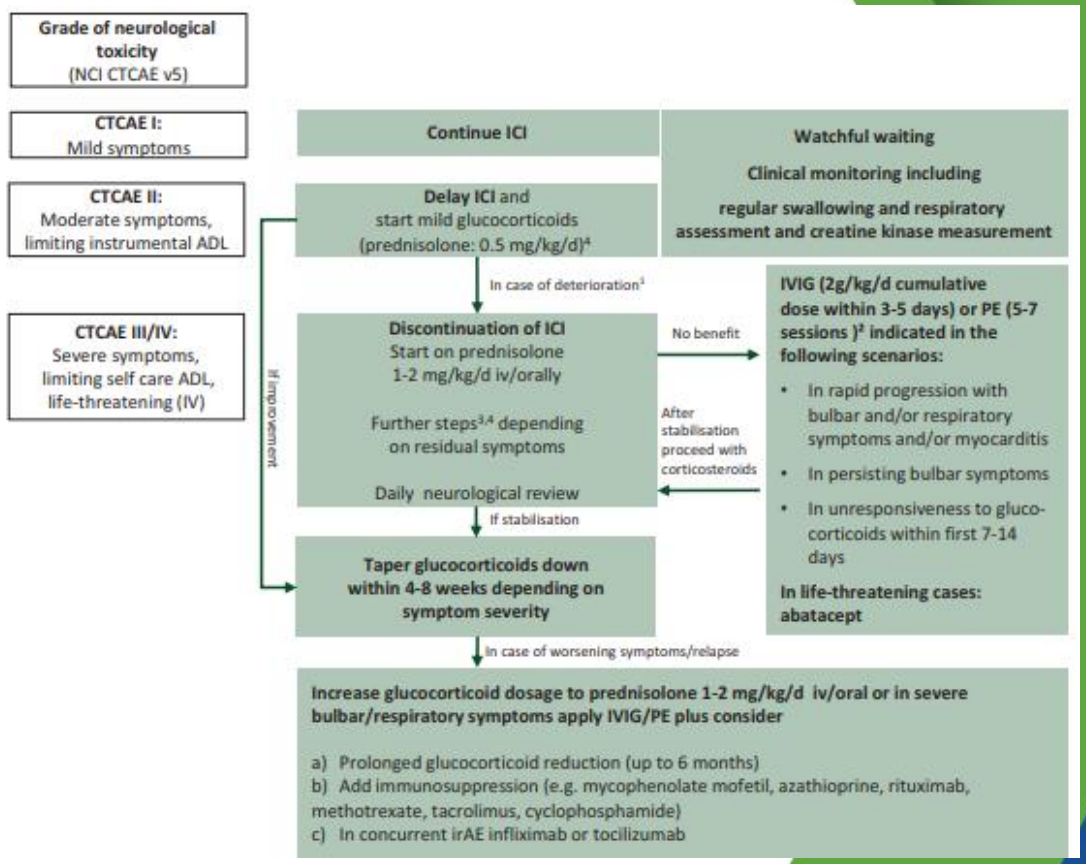
Table 1. Clinical findings in neuromuscular immune-related adverse events

Clinical findings in NMD induced by ICIs	Myasthenia gravis	Myositis
	Frequency of symptoms	
Ocular weakness (ptosis/double vision)	+++	+++
Facial weakness	++	++
Bulbar symptoms (dysarthria/dysphagia)	+++	++ 50% of the cases
Extremity weakness	+ Symmetrical proximal	++ Symmetrical proximal
Dropped head	++	+++ 70% of the cases
Limb girdle weakness	+/++	++
Pain	(+)	+++ 70% of the cases
Respiratory failure	Frequent due to diaphragm involvement or aspiration	
Reflexes	Normal	May be reduced according to paresis
Cardiac pathology	Rare in isolated MG, 10% overlapping myositis-myocarditis	++ 25%-35% myocarditis, arrhythmia
	Additional findings	
Laboratory findings: CK	Normal, elevated in myositis overlap	Markedly (fivefold to 10-fold) elevated (including troponin) up to 100×, rarely normal[a]
Cerebrospinal fluid	Normal	Normal
Antibody status	May be positive for AChR, often negative or very low titres	Negative

Jordan et al J ESMO Open 2021

Myositis/Myasthenia Gravis Treatment

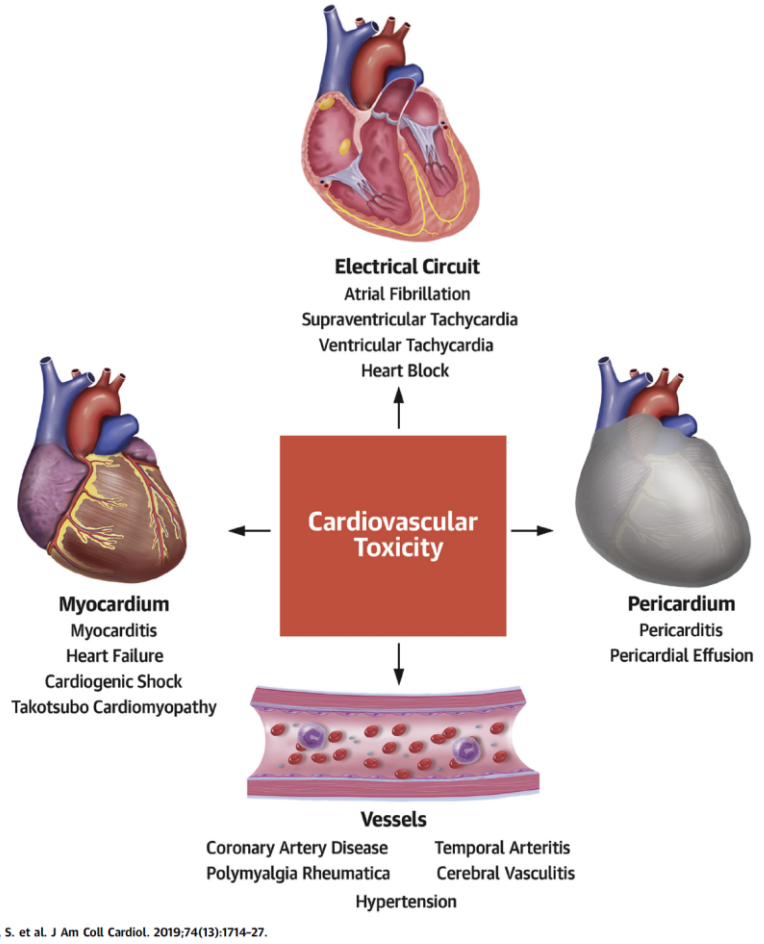
- Most patients will respond to high dose IV steroids
- IVIG and/or plasma exchange may be needed – low threshold to initiate if worsening symptoms
- Other treatments can include abatacept, mycophenolate, azathioprine, rituximab
- Prolonged treatment is often required
- In most cases, ICB will need to be permanently discontinued



Haanen et al Annals of Oncology 2022

Myocarditis

- Rare – but very high mortality (~50%)
- First reported incidence of 0.09% in safety data -> more recent registry data = 1.1%
- Can occur in up to 30% of irMyositis
- Meta-analysis of 22 studies:
  - CHF = 2.0%
  - MI = 1.0%
  - Cardiac arrest = 1.0%



Ball et al JAAC 2019

Myocarditis diagnostic criteria

IC-OS 2021 Consensus

Either pathohistological diagnosis:

Multifocal inflammatory cell infiltrates with overt cardiomyocyte loss by light microscopy of cardiac tissue samples

Or clinical diagnosis [# §]:

A troponin elevation (new, or significant change from baseline) with 1 major criterion or a troponin elevation (new, or significant change from baseline) with 2 minor criteria after exclusion of acute coronary syndrome or acute infectious myocarditis based on clinical suspicion

Major Criterion

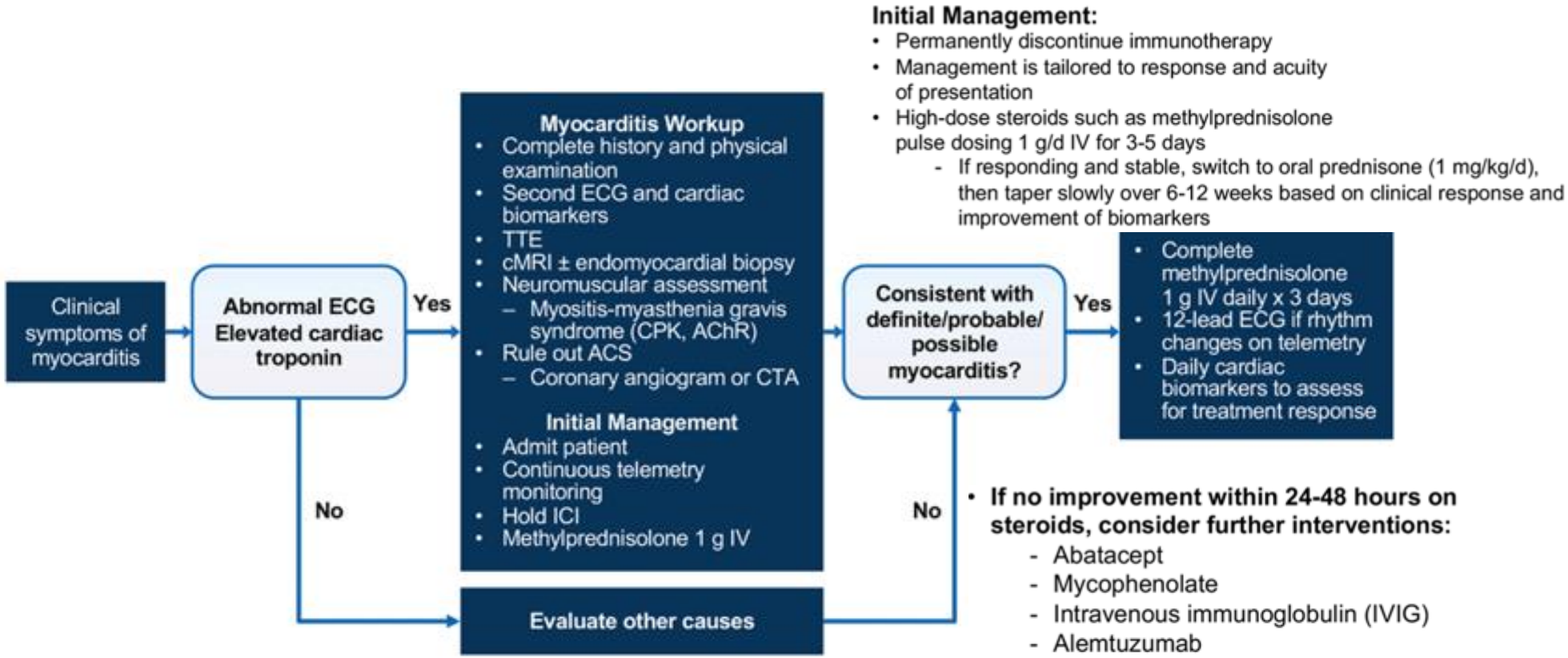
- CMR diagnostic for acute myocarditis (modified Lake Louise criteria)

Minor Criteria

- Clinical syndrome (including any one of the following: fatigue, muscle weakness, myalgias, chest pain, diplopia, ptosis, shortness of breath, orthopnea, lower extremity edema, palpitations, lightheadedness/dizziness, syncope, cardiogenic shock)
- Ventricular arrhythmia and/or new conduction system disease
- Decline in cardiac (systolic) function, with or without regional WMA in a non-Takotsubo pattern
- Other immune-related adverse events, particularly myositis, myopathy, myasthenia gravis
- Suggestive CMR (meeting some but not all of the modified Lake Louise citeria)

Herrmann et al Eur Heart J 2022

Assessment/Management



Initial Management:

- Permanently discontinue immunotherapy
- Management is tailored to response and acuity of presentation
- High-dose steroids such as methylprednisolone pulse dosing 1 g/d IV for 3-5 days
  - If responding and stable, switch to oral prednisone (1 mg/kg/d), then taper slowly over 6-12 weeks based on clinical response and improvement of biomarkers

- **If no improvement within 24-48 hours on steroids, consider further interventions:**
  - Abatacept
  - Mycophenolate
  - Intravenous immunoglobulin (IVIG)
  - Alemtuzumab
  - Infliximab (use with extreme caution in patients with reduced LVEF)
  - Antithymocyte globulin (ATG)
  - Plasmapheresis
- ICU-level monitoring
- Temporary or permanent pacing as required

Lehmann et al JAMA Cardiology 2021
NCCN Clinical Practice Guidelines

Conclusions

- Neuromuscular irAE's and Triple M syndrome carry high rates of morbidity and mortality
- Although rare, non-specific symptoms may lead to underdiagnosis
- Rapid identification and appropriate intervention can be **life-saving**!
- Close monitoring and multidisciplinary evaluation (neurology, cardiology) are needed
- Guidelines from national organizations provide excellent resources for initial management (SITC, ASCO, NCCN, ESMO etc)