Immune-Related Inflammatory Rheumatological Adverse Event Management Algorithm

Grading of Inflammatory arthritis*	Action	Follow up
Grade 1 Mild pain/stiffness	**Investigations:** • Bloods: Immunotherapy Panel including FBC, U&E, Clotting, CRP, Cortisol, ESR, ANA, Rheumatoid factor, Anti- CCP and CK **Management:** • Continue ICI therapy. • Simple analgesia e.g. Paracetamol	If a single joint affected and above measures ineffective, consider Rheumatology referral for intra-articular corticosteroid injection. **If symptoms persist ≥5 days / worsen:** • Treat as grade- 2
Grade 2 Arthralgia Moderate pain/ swelling/ morning stiffness Limitation of instrumental ADL)	**Investigations:** • Bloods as per G1 • Cardiac investigations if signs of myalgia/myositis** **Management:** • Rheumatology referral • Symptomatic management with analgesia as for mild. • Commence Prednisolone 20mg daily for 1 week, then 10mg for 2 – 4 weeks then taper. (Consider gastric protection)	**If no improvement**: • Consider imaging (US, MRI or CT of inflammatory arthritis and suspicion of metastatic lesion or septic arthritis • Consider Prednisolone 0.5 to 1 mg/kg up to max 60mg. **If static on oral steroids:** • Consider the introduction of a DMARD e.g. Methotrexate, Azathioprine, MMF, IL6R or TNF-alpha inhibitors. **If worsens:** • Treat as G3-4
Grade 3 or 4 **Severe or Life-threatening** Severe pain as ssociated with signs of inflammation, erythema, or joint swelling, irreversible joint damage (e.g erosion) disabling, limiting ADL's.	**Investigations** • As for moderate arthralgias but temporarily hold ICI **Management:** • Rheumatology referral • Naproxen 500mg BD • IV Methylprednisolone up to 2mg/kg daily + gastric protection`.	**If no improvement or worsening**: • Consider DMARDs such as Methotrexate. • If already commenced, consider introduction of additional DMARD. • Biologics can be considered on failure of DMARDs in collaboration with Rheumatology like IL-6R Inhibitors or TNF-alpha inhibitors. Note: Sulphasalazine has been associated with high levels of hypersensitivity and therefore is NOT recommended.

***Inflammatory arthritis**: Pain, swelling and stiffness in joints, typically the stiffness lasts for 60 minutes or more in the mornings, associated with impaired joint function.

Immune-Related Inflammatory Rheumatological Adverse Event Management Algorithm

Grading of Myositis**	Action	Follow up
Grade 1 Mild weakness with or without pain	**Investigations:** • Bloods: Immunotherapy Panel including FBC, U&E, LFTS, Clotting, CRP, Cortisol, ESR, ANA, Rheumatoid factor, Anti-CCP and CK, aldolase, troponins **Management:** • Continue ICI therapy. • Analgesia with paracetamol or NSAIDS	**If CK and/or aldolase elevated and patient has muscle weakness:** • Treat as grade 2.
Grade 2 Moderate weakness with or without pain, limiting age-appropriate instrumental ADLs)	**Investigations:** • As above • Consider EMG, MRI and/or biopsy, paraneoplastic screen if overlap with neurological syndromes such as myasthenia is suspected. **Management:** • Early Rheumatology/Neurology (if neurological symptoms) referral • If CK more than 3 x ULN, start prednisolone 0.5-1mg/kg. • Rule out overlapping neurological symptoms or cardiac symptoms. (Check cardiac and neurological guidelines)	**If stable / improving**: • Can restart ICI if CK normal, clinical manifestation of myositis resolved and patient on <10mg OD of Prednisolone **If worsens:** • Treat as G3-4 • NSAIDs as needed. • Might need to stop ICI permanently if objective findings of severe muscle involvement e.g. very elevated enzymes, extensive involvement as determined by EMG, MRI or histology.
Grade 3 or 4 **Severe or Life-threatening** Severe weakness with or without pain, limiting age-appropriate instrumental ADLs	**Investigations** • As above **Management:** • Admit to Hospital • Urgent Rheumatology/neurology (if neurological symptoms) referral • Start prednisolone 1mg/kg, consider methylprednisolone 1-2mg/kg or higher dose if severe compromise (weakness severely limiting mobility, cardiac, respiratory or dysphagia)	**If no improvement or worsening**: • Consider plasmapheresis (for rapid response) or IVIG (onset of action is slower). • Consider Biologics e.g. Rituximab, TNF alpha, IL6 antagonists if symptoms worsen of no improvement after 2 weeks. • Consider other Immunosuppressants - MTx/ MMF (preferred) or azathioprine for maintenance. • Can consider Tacrolimus as third line.

****Myositis:** Weakness (and sometimes pain) of proximal muscles, can be associated with rashes (in dermatomyositis), associated typically with high CK (in thousands). MRI is usually quite good for picking up muscle inflammation, PET CT is also quite useful and reviewing previous PET CT scans may be worthwhile.
Cardiac involvement, important to check Troponins and BNP. Other tests such as ECG, echo or Cardiac MRI (Read myocarditis)
Neurological history and muscle examination- Possible myasthenia autoantibodies if symptoms (EMG, anti-AChR and antistriational antibodies)

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Grading of PMR-like syndrome	Action	Follow up
Grade 1 Mild pain / stiffness	**Investigations** • Bloods: Immunotherapy Panel including FBC, U&E, LFTS (inc ALT), Clotting, CRP, Cortisol, ESR, ANA, Rheumatoid factor, Anti- CCP and CK **Management:** • Start regular analgesia	**If no response after 7 days:** • Commence Prednisolone 10-15mg once daily and review to ensure symptom *resolution within a week*. **If symptoms have improved:** • Continue to manage as Polymyalgia Rheumatica • Note patients often only need a short course (few weeks) of steroids.
Grade 2 Moderate to severe pain/stiffness Limitation of instrumental ADL	**Investigations:** • As per G1 • Cardiac investigations if signs of myalgia/myositis** **Management:** • Rheumatology referral • Prednisolone 10-20 mg/day for grade 2 or more symptoms, progressively tapered when symptoms improved.	**For corticosteroid dependent/ refractory cases:** • Rheumatology referral • Consider methotrexate or IL-6R inhibitors.

Polymyalgia type syndrome: Pain and morning stiffness (usually lasting 60 minutes or more) in proximal muscles typically shoulder and hip girdles, not typically associated with weakness or loss of range of movements.

Giant cell arteritis: New onset headaches, temporal pain, scalp tenderness, jaw claudication, visual symptoms such as amaurosis, reduced vision, diplopia, field loss. {Typically associated with high CRP, but ~5% have normal CRP; can also have PMR type symptoms].

Myopathy: Usually, proximal muscle weakness not associated with high CK values, Lot of caveats – can be distal as well, some genetic forms associated with high CK, steroid myopathy would be the commonest form of this. Thyroid myopathy can also be seen.

Myositis: Typically presents with proximal muscle weakness, but not much pain. Associated with high CK values in the majority, sometimes MRI of proximal muscles/ biopsy needed for diagnosis. Can also cause cardiac involvement, important to check Troponins and BNP.

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