Guidelines for management of immune checkpoint inhibitor toxicities

General Principles

Note: Immune checkpoint inhibitors include anti-PD-1 (nivolumab, pembrolizumab, cemiplimab), anti-PD-L1 (atezolizumab, avelumab, durvalumab), and anti-CTLA-4 (ipilimumab, tremelimumab) agents.

Diagnostic workup:

- Consultation with appropriate specialists (e.g. gastroenterology for suspected colitis) and/or immuno-oncology experienced oncologists is appropriate in serious cases and in those with diagnostic uncertainty.
- Tissue diagnosis is potentially helpful for diagnostic confirmation in many cases (e.g. colonoscopy/biopsy for suspected colitis) but unless there is substantial diagnostic uncertainty or indolent presentation, empiric corticosteroids should not be delayed, particularly in clinically serious cases.

Management:

- Treatment for immune checkpoint inhibitor (ICI) toxicities is usually guided by grading outlined in the Common Terminology Criteria for Adverse Events version 4.03. https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf
- Except where noted below, toxicities are treated with the following principles:
    - Grade 1 toxicities usually are treated with symptomatic management and continuation of the ICI with close monitoring.
    - Grade 2 toxicities are usually treated with close monitoring/supportive care, holding of ICI, and initiation of steroids as for grade 3 if the toxicity persists.
    - Grade 3 toxicities are usually treated with corticosteroids, prednisone 1-2mg/kg/daily or equivalent with 4-6 week taper, holding ICI, and close monitoring/supportive care. ICI rechallenge may be considered in certain circumstances as noted below.
    - Grade 4 toxicities are usually treated as above and ICI rechallenge is contraindicated.
    - High-dose steroids are usually continued at high dose (prednisone 1-2mg/kg/daily) until symptoms improve to grade 0-1 and then tapered over 4-6 weeks.
    - If symptoms do not improve with steroids over 3-7 days, or flare during steroid taper, additional disease-specific immunosuppressants are indicated.

Colitis/enteritis

Diagnostic workup:

- Presents with watery diarrhea most frequently, less often abdominal cramping or bleeding (~10%).
- Labs: Clostridium difficile, stool cultures, +/- ova and parasites, viral testing, tissue transglutaminase
- Imaging: +/- Abdominal/pelvis CT which may show bowel inflammation
- Other: Colonoscopy/flexible sigmoidoscopy may confirm diagnosis and rule out other causes. Ulcerations on endoscopic exam predicts need for infliximab. Gastroenterology consultation is recommended for prolonged cases, diagnostic uncertainty, or in patients requiring inpatient admission. Treatment with steroids should not be withheld pending endoscopic evaluation in highly probable cases.

Management:

- Grade 1 (1-3 stools per day above baseline). Continue or temporarily hold ICI, loperamide if needed.
- Grade 2 (4-6 stools per day above baseline). Hold ICI until grade 1, supportive care with loperamide if needed, hydration, electrolyte monitoring. If persistent (>3 days) treat as grade 3.
- Grade 3 (>6 stools per day above baseline). Hold ICI, permanently discontinue anti-CTLA-4, may consider resuming anti-PD-1/PD-L1 when grade 1. Prednisone 1-2mg/kg daily and taper over 4 weeks. Admit to hospital if dehydration or electrolyte imbalance. Infliximab 5mg/kg if persistent symptoms for 3-5 days, consider infliximab if ulcerations are present on colonoscopy.
- Grade 4 – as above but permanently discontinue ICI, treat with IV steroids, consider earlier infliximab (after 2-3 days).
- Colitis flares: If colitis flares during steroid taper or after steroid, give infliximab. For cases refractory to infliximab, consider vedolizumab (requires GI consult).

<u>Pneumonitis</u>

Diagnostic workup:

- Presents most often with dry cough +/- hypoxia but may also less often present with fever, wheezing, occasionally productive cough.
- Imaging: Chest x-ray, chest CT without contrast. May present as bilateral ground-glass opacities but may also appear nodular or have a focal appearance.
- Other: Low-threshold for pulmonary consultation +/- infectious disease, +/- PFTs

Management:

- Grade 1 (asymptomatic, pneumonitis observed on imaging). Consider continuing therapy if with close monitoring if relatively minimal inflammation. Consider holding ICI if extensive involvement (e.g. multilobar involvement, extensive groundglass opacities), repeating imaging in 4 weeks, resume if improvement. Monitor q1-2 weeks with chest x-ray and oxygen saturation.

- Grade 2 (mild symptoms). Hold ICI until grade 1. Give prednisone 1-2mg/kg with taper over 4-6 weeks. Consider bronchoscopy, consider empiric antibiotics. Monitor up to q72 hours until improvement; if none treat as grade 3.
- Grade 3-4 (severe symptoms). Permanently discontinue ICI, admit to hospital, give IV methylprednisolone 1-2mg/kg/day. If no improvement in 48 hours add infliximab 5mg/kg or mycophenolate mofetil 1g twice daily, or intravenous immunoglobulin (IVIG) x 5 days. Taper steroids over 4-6 weeks. Consider bronchoscopy.

Hepatitis

Diagnostic workup:

- Usually asymptomatic.
- Consider other causes, including viral serologies, iron studies, liver ultrasound. Tends to present with AST/ALT elevations predominantly rather than bilirubin/alkaline phosphatase.

Management:

- Grade 1 (AST or ALT ULN – 3x ULN): Continue ICI, monitor labs closely.
- Grade 2 (AST or ALT 3 – 5x ULN): Hold ICI, give prednisone 0.5 – 1mg/kg/day if persists >3-5 days. Monitor labs closely.
- Grade 3-4 (AST or ALT 5-20x ULN): Permanently discontinue ICI, give prednisone 1-2mg/kg daily or equivalent with taper over 4-6 weeks, give mycophenolate mofetil (MMF) 1g twice daily if no improvement after 3 days or flares. Continue MMF until prednisone is tapered to 10mg or less.
- Grade 4 (AST or ALT >20x ULN): As with grade 3; use methylprednisolone 2mg/kg as initial dose, consider hepatology evaluation. Refractory cases may respond to anti-thymocyte globulin (ATG).

Skin toxicities

Diagnostic workup:

- Wide variety of skin eruptions +/- pruritus, most commonly on trunk and extremities.
- Rule out other causes (other drug effect, infection, flare of existing dermatologic condition).
- Skin biopsy should be done if diagnostic uncertainty, blistering, or concern for Stevens Johnson syndrome/toxic epidermal necrolysis (SJS/TEN).

Management:

- Grade 1 (<10% body surface area [BSA]): Continue ICI. May use topical emollients if dry skin, or topical steroids (hydrocortisone 2.5% ointment to face or triamcinolone 0.1% ointment in 454g jar) if itching.

- Grade 2 (10-30% BSA): Consider holding ICI until grade 1. Strongly consider derm referral. Use skin emollients, topical moderate/high potency corticosteroids, oral antihistamines. If persistent and refractory to topicals consider short dose of low dose prednisone (e.g. prednisone 20-40mg x 5 days) or prednisone 1mg/kg tapered over 4 weeks.
- Grade 3 (>30% BSA, limiting ADLs): Hold ICI until grade 1, topical emollients, oral antihistamines, high-potency topical steroids. Give prednisone 1mg/kg or equivalent, taper over 4 weeks. Derm referral to consider steroid-sparing agent.
- Grade 4: As with grade 3, admit to hospital and obtain derm consult, consider permanent discontinuation of ICI.
- For **SJS/TEN**: As with grade 4 above, also consider IVIG or cyclosporine in addition to steroids, admit to burn unit with close monitoring of fluids/electrolytes.
- **Pruritus without rash**: Treat with oral antihistamines, pregabalin. Consider dermatology referral.
- **Vitiligo**: No treatment necessary. As with other skin toxicities, may correlate with improved outcome with immunotherapy. Review strict photoprotections.

Hypophysitis/hypopituitarism/adrenal insufficiency

Diagnostic workup:

- Presents most often with fatigue +/- hypotension and electrolyte abnormalities, may present with central headache +/- double vision if hypophysitis
- Labs: cortisol, ACTH, TSH, free T4, electrolytes; +/- ACTH stimulation if indeterminate, +/- LH, FSH, testosterone, estrogen.
- Imaging: Brain MRI with pituitary windows if headaches or vision changes, or may consider if laboratory evaluation suggests central hormone deficiency (low ACTH or TSH in setting of low cortisol or free T4).

Management

- Consider holding ICI until stabilized on hormone regimen. Start hydrocortisone 15mg qam and 10mg qpm, levothyroxine if hypothyroid (to start several days after steroids).
- If severe symptoms consider 1-2 weeks of prednisone 1mg/kg/day, IV fluids.
- Consider endocrinology consultation. Often requires lifelong hormone replacement.
- OK to resume ICI after hormone regimen initiated.

Hypo/hyperthyroidism

Diagnostic workup:

- TSH, FT4, T3. TSH receptor antibodies if suspicion for Graves disease.

Management:

- Hypothyroidism: Continue ICI. Initiate thyroid hormone replacement if symptomatic or if TSH >10mIU/L persistent over 4 weeks. Monitor TSH every 6 weeks at least.
- Hyperthyroidism: Continue ICI, may consider holding while symptomatic. Beta blocker or hydration if symptomatic. Consider endocrine consult. Persistent cases (>6 weeks) or concern for thyroid storm obtain endocrine consult and consider potassium iodide, methimazole, or propylthiouricil. Monitor thyroid function; will likely progress to hypothyroid. Steroids not indicated.

Diabetes (type 1)

Diagnostic workup:

- Glucose, anion gap, urine ketones, insulin, c-peptide, +/- anti-islet cell/insulin/glutamic acid decarboxylase antibodies.

Management:

- Consider holding ICI until glucose control but may resume thereafter.
- Endocrine consultation, insulin therapy, hospital admission (mandatory for DKA). Steroids are not indicated.

Myocarditis

Diagnostic workup:

- Labs: Troponin, brain natriuretic peptide (BNP)
- Imaging: Echocardiogram, cardiac MRI encouraged
- Other: EKG, consider cardiac catheterization to rule out ischemia, consider myocardial biopsy
- Symptoms are often non-specific but often presents with arrhythmias, chest pain, shortness of breath.

Management:

- Asymptomatic troponin elevations: Hold ICI, cardiology consult, EKG, echo and/or cardiac MRI. Rule out other causes of troponin elevation (e.g. ischemia). If persistent may consider prednisone 1-2mg/kg/day and treat as symptomatic.
- Grade 2-4 (symptomatic): Admit to hospital. Cardiology consult and telemetry. Hold ICI, prednisone 1-2mg/kg (mild symptoms) or methylprednisolone 1000mg IV daily if arrhythmias or severe symptoms. Obtain echo, serial ekg, cardiac MRI, consider cardiac catheterization and myocardial biopsy. Consider adding other immunosuppressant (mycophenolate mofetil, IVIG, ATG). Strongly consider CCU admission, aggressive treatment, percutaneous pacemaker available/early defibrillator placement due to high incidence of heart block and ventricular arrhythmias which may be fatal.

Neurologic toxicities

Diagnostic workup:

- Most common presentations are myasthenia gravis, meningo-encephalitis, Guillain-Barre Syndrome, peripheral neuropathy, and transverse myelitis.
- Myasthenia gravis: Acetylcholine receptor (AchR), antistriated muscle antibodies, PFTs, CK and troponin to rule out myocarditis/myositis, consider MRI brain/spine, consider electromyogram/nerve conduction studies (EMG/NCS).
- Guillain-Barre Syndrome: MRI spine with/without contrast, lumbar puncture, antiganglioside antibody tests, EMG/NCS, neuro-checks, PFTs.
- Peripheral neuropathy: B12, folate, TSH, HIV, MRI spine, +/- EMG/NCS
- Meningitis/Encephalitis: MRI brain, lumbar puncture with cell count, protein, cultures, herpes simplex virus (HSV) and other viral PCRs.
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Management:

- Management is similar to that of primary condition not associated with ICI, steroids are generally added to standard disease-specific therapies.
- Myasthenia Gravis: Neurology consult, hold ICI, pyridostigmine, prednisone 1-2mg/kg/day. If grade 3-4 add IVIG or plasmapheresis for 5 days. Close neurologic monitoring.
- Guillain-Barre Syndrome: Neurology consult, discontinue ICI, intensive care unit, methylprednisolone 1-2mg/kg/daily trial, IVIG or plasmapheresis for 5 days, frequent neurochecks.
- Peripheral neuropathy: If grade 1-2, hold ICI +/- trial of prednisone 0.5-1mg/kg/daily, neuropathic pain agents as needed. If grade 3-4, discontinue ICI, admit to hospital, consult neurology, methylprednisolone 2mg/kg and consider similar management as Guillain Barre Syndrome.
- Meningitis/Encephalitis: Neurology consult, admit to hospital, consider empiric antibiotics/acyclovir, prednisone 1mg/kg (if meningitis or very mild symptoms) or methylprednisolone 1000mg/day (if encephalitis with severe symptoms, extensive brain involvement, or unresponsive to initial steroid trial)

Hematologic Toxicities

Note: This section focuses on the most common (albeit still uncommon, affecting <1% of patients) hematologic toxicities. Other hematologic events have been noted rarely, including hemophagocytic lymphangiohistiocytosis (HLH), pure red cell aplasia, thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), and acquired hemophilia. These disorders should be diagnosed and treated as their primary conditions with consideration of adding corticosteroids. See guidelines below for additional information.

Diagnostic workup:

Hemolytic anemia: CBC, LDH, haptoglobin, retic, bilirubin, peripheral smear, Coombs, SPEP, G6PD, history for common drugs, coagulation studies.

Immune thrombocytopenic purpura: CBC, peripheral smear, retic, HIV, hepatitis B/C, H. pylori; +/- bone marrow biopsy, Coombs.

Aplastic anemia: CBC, peripheral smear, retic, viral studies (cytomegalovirus, human herpes virus-6, Epstein-Barr virus, parvovirus), bone marrow biopsy, flow cytometry for glycosylphosphatidylinositol-anchored proteins.

Management:

Hemolytic anemia: Heme consult, prednisone 1-2mg/kg, discontinue ICI, transfusion as needed, folate supplementation. Consider rituximab, IVIG, cyclosporine, MMF if no improvement.

Immune thrombocytopenic purpura: For grade 1 – close monitoring and continue ICI; for grade 2+ hold ICI, prednisone 1-2mg/kg/daily. Consider IVIG 1g x1 with optional repeating if no improvement or need rapid platelet rise. Refractory cases can receive ritixumab, splenectomy, thrombopoietin receptor agonists.

Aplastic anemia: Heme consult, hold ICI, growth factor support, close laboratory monitoring, consider horse ATG and cyclosporine, if no response give rabbit ATG plus alemtuzumab. Role of steroids is unclear.

Nephritis

Diagnostic workup:

- Exclude other causes, urinalysis, urine eosinophils, nephrology consult, +/- renal biopsy. Most commonly renal failure is due to other causes.

Management:

- If grade 1 (creatinine increase by <1.5x ULN) consider holding ICI. For grade 2+, hold ICI, nephrology consult, prednisone 1-2mg/kg. If no improvement consider mycophenolate mofetil.
- Note: nephrotic syndrome has also been uncommonly described, and is treated with steroids. Rituximab has been used effectively in steroid-refractory cases.

Inflammatory arthritis

Diagnostic workup:

- Rheumatologic exam, plain films of affected joints, consider ANA, RF, anti-CCP, ESR/CRP. Consider MRI for severe cases to rule out other causes. Consider rheumatology referral for severe or refractory cases.

Management:

- Grade 1: continue ICI, acetaminophen and/or NSAIDs as needed
- Grade 2 (moderate pain, signs of inflammation, limiting iADLs): Hold ICI, escalate analgesia, consider brief burst of prednisone (e.g. 20mg/daily x 5 days). If no improvement may give prednisone 10-20mg/daily x4-6 weeks, resume ICI when grade 1 and on 10mg or less; rheumatolody consult and consider disease modifying anti-rheumatic drug (DMARD; e.g. hydroxychloroquine, methotrexate) if unable to lower prednisone dose.
- Grade 3: Hold ICI, prednisone 0.5-1mg/kg/daily, rheum consult and DMARD if refractory.

Polymyalgia Rheumatica-like syndrome

Diagnostic workup:

- ESR, CRP, CK, evaluate for signs of temporal arteritis.

Management:

- Similar to arthritis above, although may consider tocilizumab for refractory cases.

Myositis

Diagnostic workup:

- CK, aldolase, AST, ALT, LDH, troponin +/- other cardiac testing (to rule out myocardial involvement), consider EMG, MRI, biopsy if diagnostic uncertainty.

Management:

- Grade 1 (mild pain): Continue ICI unless CK elevated and weakness present, then treat as grade 2.
- Grade 2 (moderate pain): Hold ICI, give NSAIDs, rheum/neuro consult, prednisone 0.5-1mg/kg if CK elevated 3x ULN. Treat as grade 3 if no improvement.
- Grade 3-4: Hold ICI, rheumatology/neurology consult, prednisone 1-2mg/kg/daily, consider plasmapheresis or IVIG. Consider mycophenolate mofetil, ritixumab, methotrexate if no response.

Disclaimer: This document is not intended to serve as a complete resource for management of ICI toxicities and does not list all possible toxicities or scenarios encountered with ICI. Please see **Sources** below for more complete information.

1) ASCO guidelines; Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. Brahmer et al J Clin Oncol. 2018 Jun 10;36(17):1714-1768. https://www.ncbi.nlm.nih.gov/pubmed/29442540

2) SITC guidelines; Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. Puzanov et al J Immunother Cancer. 2017 Nov 21;5(1):95. https://www.ncbi.nlm.nih.gov/pubmed/29162153

Abbreviations:

ACTH: Adrenocorticotrophic hormone; ALT: Alanine aminotransferase; ANA: anti-nuclear antibody; AST: Aspartate aminotransferate; CCP: cyclic citrullinated peptide; CK: creatine kinase; CRP: C-related peptide; CTLA: Cytotoxic T lymphocyte antigen-4; ESR: erythrocyte sedimentation rate; FSH: follicle stimulating hormone; G6PD: glucose-6-phosphate dehydrogenase; LDH: Lactate dehydrogenase; LH: Leutinizing hormone; NSAIDs: Nonsteroidal anti-inflammatory drugs; PD-1: Programmed death-1; PD-L1: Programmed death ligand-1; PFTs: Pulmonary function tests; RF: Rheumatoid factor; SPEP: serum protein electrophoresis; TSH: thyroid stimulating hormone; ULN: Upper limit of normal;