



# Management of Immune-related Adverse Events

PRACTICE ESSENTIALS FOR THE ONCOLOGY CLINICIAN

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## Endocrine

- Hypothyroidism
- Hyperthyroidism
- Adrenal insufficiency
- Hypophysitis
- Diabetes

## Lung

- Pneumonitis

## Gastrointestinal

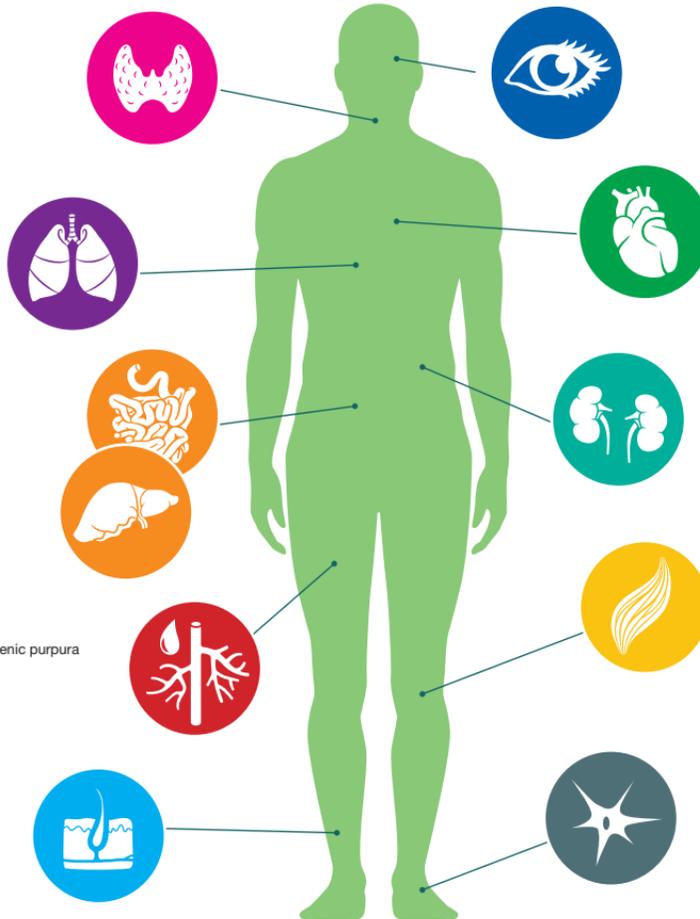
- Colitis
- Hepatitis

## Hematologic

- Autoimmune hemolytic anemia
- Acquired thrombotic thrombocytopenic purpura
- Hemolytic uremic syndrome
- Aplastic anemia
- Lymphopenia
- Immune thrombocytopenia
- Acquired hemophilia

## Skin

- Rash
- Bullous dermatoses
- Severe cutaneous adverse reaction



## Ocular

- Uveitis/Iritis
- Episcleritis
- Blepharitis

## Cardiovascular

- Myocarditis
- Venous thromboembolism

## Renal

- Nephritis
- Symptomatic nephritis

## Musculoskeletal

- Inflammatory arthritis
- Myositis
- Polymyalgia-like syndrome

## Nervous System

- Myasthenia Gravis
- Guillain-Barré Syndrome
- Peripheral neuropathy
- Autonomic neuropathy
- Aseptic meningitis
- Encephalitis
- Transverse myelitis

## Management of Immune-related Adverse Events (irAEs) in Adult Patients with Cancer Treated with Immune Checkpoint Inhibitors (ICIs)

The following recommendations in this pocket guide are from the 2018 American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) Practice Guidelines for the Management of Immune-related Adverse Events.<sup>1,2</sup>

*Note: These recommendations are current as of the date of original publication (February 14, 2018). Please consult the ASCO and NCCN practice guideline websites for any revisions or updates to these guidelines.*

<sup>1</sup>Brahmer J, Lacchetti C, Schneider BJJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2018;14(4):247-249.

<sup>2</sup>NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) in partnership with the American Society of Clinical Oncology (ASCO): Management of Immunotherapy-Related Toxicities (Immune Checkpoint Inhibitor-Related Toxicities), v1.2018. National Comprehensive Cancer Network website. [https://www.nccn.org/professionals/physician\\_gls/pdf/immunotherapy.pdf](https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf). February 14, 2018.

### ASCO/NCCN General Recommendations for irAE Management

- Patient and family caregivers should receive timely and up-to-date education about immunotherapies, their mechanism of action, and the clinical profile of possible irAEs prior to initiating therapy and throughout treatment and survivorship
- There should be a high level of suspicion that new symptoms are treatment related
- In general, ICI therapy should be continued with close monitoring for grade 1 toxicities, with the exception of some neurologic, hematologic, and cardiac toxicities
- Hold ICIs for most grade 2 toxicities and consider resuming when symptoms and/or laboratory values revert to grade 1 or less. Corticosteroids (initial dose of 0.5 to 1 mg/kg/day of prednisone or equivalent) may be administered
- Hold ICIs for grade 3 toxicities and initiate high-dose corticosteroids (prednisone 1 to 2 mg/kg/day or methylprednisolone IV 1 to 2 mg/kg/day). Corticosteroids should be tapered over the course of at least 4 to 6 weeks. If symptoms do not improve within 48 to 72 hours of high-dose corticosteroid, infliximab may be offered for some toxicities
- When symptoms and/or laboratory values revert to grade 1 or less, rechallenging with ICIs may be offered; however, caution is advised, especially in those patients with early-onset irAEs. Dose adjustments are not recommended
- In general, grade 4 toxicities warrant permanent discontinuation of ICIs, with the exception of endocrinopathies that have been controlled by hormone replacement

Toxicity	irAE	Page
 <b>Skin</b>	Rash/Inflammatory Dermatitis	<b>6</b>
	Bullous Dermatoses	<b>8</b>
	Severe Cutaneous Adverse Reactions (SCARs)	<b>11</b>
 <b>Gastrointestinal</b>	Colitis	<b>14</b>
	Hepatitis	<b>18</b>
 <b>Lung</b>	Pneumonitis	<b>21</b>
 <b>Endocrine</b>	Primary Hypothyroidism	<b>24</b>
	Hyperthyroidism	<b>25</b>
	Primary Adrenal Insufficiency	<b>27</b>
	Hypophysitis	<b>29</b>
	Diabetes	<b>30</b>
 <b>Musculoskeletal</b>	Inflammatory Arthritis	<b>12</b>
	Myositis	<b>33</b>
	Polymyalgia-like Syndrome	<b>35</b>
 <b>Renal</b>	Nephritis	<b>37</b>
	Symptomatic Nephritis	<b>40</b>

Toxicity	irAE	Page
 <b>Nervous System</b>	Myasthenia Gravis	42
	Guillain-Barré Syndrome	44
	Peripheral Neuropathy	46
	Autonomic Neuropathy	48
	Aseptic Meningitis	49
	Encephalitis	50
	Transverse Myelitis	51
 <b>Hematologic</b>	Autoimmune Hemolytic Anemia	52
	Acquired Thrombotic Thrombocytopenic Purpura	54
	Hemolytic Uremic Syndrome	56
	Aplastic Anemia	58
	Lymphopenia	60
	Immune Thrombocytopenia	61
	Acquired Hemophilia	63
 <b>Cardiovascular</b>	Myocarditis, Pericarditis, Arrhythmias, Impaired Ventricular Function with Heart Failure and Vasculitis	65
	Venous Thromboembolism	67
 <b>Ocular</b>	Uveitis/Iritis	70
	Episcleritis	71
	Blepharitis	72



# SKIN TOXICITIES

## Rash/Inflammatory Dermatitis

**Definition:** Erythema multiformeminor (a targetoid reaction in the skin and mucous membranes usually triggered by infections, such as herpes simplex viruses, but can be associated with an immune-related drug eruption and if progresses to erythema multiformemajor, it can be a harbinger of SCAR, such as SJS), lichenoid (resembling the flat-topped, polygonal, and sometimes scaly or hypertrophic lesions of lichen-planus), eczematous (inflammatory dermatitis characterized by pruritic, erythematous, scaly, or crusted papules or plaques on the skin, which is vulnerable to superinfection, psoriasiform [resembling the well-demarcated, erythematous, and scaly papules and plaques of psoriasis], morbilliform [a nonpustular, nonbullous measles-like exanthematous rash of the skin often referred to as “maculopapular” and without systemic symptoms or laboratory abnormalities, excluding occasional isolated peripheral eosinophilia, palmoplantar erythrodysesthesia [hand-foot syndrome; redness, numbness, burning, itching, and superficial desquamation of the palms and soles], neutrophilic dermatoses [eg, Sweet syndrome], and others).

### Diagnostic Work-up:

- Pertinent history and physical exam
- Rule out any other etiology of the skin problem, such as an infection, an effect of another drug or a skin condition linked to another systemic disease or unrelated primary skin disorder
- If needed, a biological checkup including a blood cell count, liver and kidney tests
- Directed serologic studies if an autoimmune condition is suspected, such as lupus or dermatomyositis: a screening antinuclear antibody test, SS-A/Anti-Ro, SS-B/Anti-La if predominantly photodistributed/photosensitivity, anti-histone, double stranded-DNA and other relevant serologies. Consider expanding serologic studies or diagnostic work-up if other autoimmune conditions are considered based on signs, symptoms
- Skin biopsy
- Consider clinical monitoring with use of serial clinical photography
- Review full list of patient medications to rule out other drug-induced cause for photosensitivity

## Rash/Inflammatory Dermatitis

Grading*	Management
<p><b>G1:</b> Symptoms do not affect the quality of life or controlled with topical regimen and/or oral antipruritic</p>	<ul style="list-style-type: none"> <li>• Continue ICI</li> <li>• Treat with topical emollients and/or mild-moderate potency topical corticosteroids</li> <li>• Counsel patients to avoid skin irritants and sun exposure</li> </ul>
<p><b>G2:</b> Inflammatory reaction that affects quality of life and requires intervention based on diagnosis</p>	<ul style="list-style-type: none"> <li>• Consider holding ICI and monitor weekly for improvement. If not resolved, interrupt treatment until skin AE has reverted to grade 1</li> <li>• Consider initiating prednisone (or equivalent) at dosing 1 mg/kg/day tapering over at least 4 weeks</li> <li>• In addition, treat with topical emollients, oral antihistamines and medium- to high-potency topical corticosteroids</li> </ul>
<p><b>G3:</b> As grade 2 but with failure to respond to indicated interventions for a grade 2 dermatitis</p>	<ul style="list-style-type: none"> <li>• Hold ICI therapy and consult with dermatology to determine appropriateness of resuming</li> <li>• Treat with topical emollients, oral antihistamines and high-potency topical corticosteroids</li> <li>• Initiate (methyl)prednisolone (or equivalent) 1-2 mg/kg/day, tapering over at least 4 weeks</li> </ul>
<p><b>G4:</b> All severe rashes unmanageable with prior interventions and intolerable</p>	<ul style="list-style-type: none"> <li>• Immediately hold ICI and consult dermatology to determine appropriateness of resuming ICI therapy upon resolution of skin toxicity and once corticosteroids are reduced to prednisone (or equivalent) 10 mg or less.</li> <li>• Systemic corticosteroids: IV (methyl)prednisolone (or equivalent) 1-2 mg/kg/day, with slow tapering when the toxicity resolves</li> <li>• Monitor closely for progression to severe cutaneous adverse reaction</li> <li>• Should admit patient immediately with direct oncology involvement and with an urgent consult by dermatology</li> <li>• Consider alternative antineoplastic therapy over resuming ICIs if the skin irAE does not resolve to grade 1 or less. If ICIs are the patient's only option, consider restarting once these side effects have resolved to a grade 1 level</li> </ul>

\*Grading according to CTCAE criteria is a challenge for skin. Instead, severity may be based on BSA, tolerability, morbidity, and duration.

## Bullous Dermatoses

**Definition:** Including bullous pemphigoid or other autoimmune bullous dermatoses, bullous drug reaction

### Diagnostic Work-up:

- Physical exam
- Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease
- If needed, a biological checkup, including a blood cell count, liver and kidney tests; consider serum antibody tests to rule out bullous pemphigoid or, under the guidance of dermatology, sending patient serum for indirect immunofluorescent testing to rule out other autoimmune blistering diseases
- Referral to dermatology for blisters that are not explained by infectious or transient other causes (eg, herpes simplex, herpes zoster, bullous impetigo, bullous insect bite, friction or pressure blister)
- Consider skin biopsy (both hematoxylin and eosin evaluation of lesional skin and direct immunofluorescence evaluation of perilesional skin)

## Bullous Dermatoses

Grading	Management
<b>G1:</b> Asymptomatic, blisters covering <10% BSA and no associated erythema	<ul style="list-style-type: none"><li>• If blisters are &lt;10% BSA, are asymptomatic and non-inflammatory (such as the case with friction blisters or pressure blisters), cessation of ICI is not necessary and only observation/local wound care is warranted</li><li>• When symptomatic bullae or erosions, which are deroofed vesicles or bullae, are noted on the skin or mucosal surfaces, the cutaneous irAE is by definition considered at least grade 2</li><li>• See grade 2 management recommendations</li></ul>

**G2:** Blistering that affects quality of life and require intervention based on diagnosis not meeting criteria for >grade 2. Blisters covering 10%-30% BSA

- Hold ICI therapy and consult with dermatology for work-up and to determine appropriateness of resuming
- Attention given to general local wound care, which includes plain petrolatum ointment and bandages or plain petrolatum ointment gauze and bandage over any open erosions, which are left over on the skin after the blister has popped or if the roof of the blister easily sloughs off
- Counsel patients to avoid skin irritants and overexposure to sun, wear protective clothing, use sunscreens
- Work-up for autoimmune bullous disease as above
- Initiate class 1 high-potency topical steroid (eg, clobetasol, betamethasone or equivalent), and reassess every 3 days for progression or improvement
- Low threshold to initiate treatment with prednisone (or equivalent) at 0.5-1 mg/kg dosing and taper over at least 4 weeks
- Monitor patients with grade 2 irAE's closely for progression to involvement of greater body surface area and/or mucous membrane involvement. Consider following patients closely using serial photography

Primer on monitoring for complicated cutaneous adverse drug reactions:

- Review of systems: Skin pain (like a sunburn), fevers, malaise, myalgias, arthralgias, abdominal pain, ocular discomfort or photophobia, sores or discomfort in the nares, sores or discomfort in the oropharynx, odynophagia, hoarseness, dysuria, sores or discomfort in the vaginal area for women or involving the meatus of the penis for men, sores in the perianal area or pain with bowel movements
- Physical exam: Include vital signs and a full skin exam specifically evaluating all skin surfaces and mucous membranes (eyes, nares, oropharynx, genitals and perianal area). Assess for lymphadenopathy, facial or distal extremity swelling (may be signs of DIHS/DRESS). Assess for pustules or blisters or erosions in addition to areas of “dusky erythema” which may feel painful to palpation. To assess for a positive Nikolsky sign, place a gloved finger tangentially over erythematous skin and apply friction parallel to the skin surface. Nikolsky sign is positive if this results in detached or sloughing epidermis demonstrating poor attachment of the epidermis to the dermis, which is the case in some autoimmune disorders (eg, pemphigus) and SJS/TEN

**G3:** Skin sloughing covering >30% BSA with associated pain and limiting self-care ADL

- Hold ICI therapy and consult with dermatology to determine appropriateness of resuming
- Administer IV (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering over at least 4 weeks
- If bullous pemphigoid is diagnosed, it may be possible to avoid longterm use of systemic corticosteroids and treat with rituximab, as an alternative approach to treating the irAE
- Seek infectious disease consultation if patient might have secondary cellulitis or if patient has other infection risk factors such as neutropenia, etc.

**G4:** Blisters covering >30% BSA with associated fluid or electrolyte abnormalities

- Permanently discontinue ICI
- Admit patient immediately and place under supervision of a dermatologist
- Administer IV (methyl)prednisolone (or equivalent) 1–2mg/kg with tapering over at least 4 weeks when the toxicity resolves
- If bullous pemphigoid is diagnosed, it may be possible to avoid long-term use of systemic corticosteroids and treat with rituximab, as an alternative approach to treating the irAE
- Seek infectious disease consultation if patient might have secondary cellulitis or if patient has other infection risk factors such as neutropenia, etc.

**Severe Cutaneous Adverse Reactions (SCARs)**, including Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS)/Drug-induced Hypersensitivity Syndrome (DIHS)

**Definition:** Severe changes in either structure or functions of skin, the appendages or the mucous membranes due to a drug

**Diagnostic Work-up:**

- Total body skin exam with attention to examining all mucous membranes, as well as complete review of systems
- Rule out any other etiology of the skin problem, such as an infection, an effect of another drug or a skin condition linked to another systemic disease
- A biological checkup including a complete blood count (CBC) with differential test (DIFF), liver and kidney function tests, including urinalysis (UA) in addition to the blood work. If the patient is febrile, blood cultures should be considered, as well
- Skin biopsies to assess for full thickness epidermal necrosis, as is seen in SJS/TEN, as well as other possible etiologies like paraneoplastic pemphigus or other autoimmune blistering dermatoses or other drug reactions, such as acute generalized exanthematous pustulosis (AGEP)
- Consider following patients closely using serial clinical photography
- If mucous membrane involvement or blistering is noted on the skin, consider early admission to a burn center for further monitoring and management

Primer on monitoring for complicated cutaneous adverse drug reactions:

- Review of systems: Skin pain (like a sunburn), fevers, malaise, myalgias, arthralgias, abdominal pain, ocular discomfort or photophobia, sores or discomfort in the nares, sores or discomfort in the oropharynx, odynophagia, hoarseness, dysuria, sores or discomfort in the vaginal area for women or involving the meatus of the penis for men, sores in the perianal area or pain with bowel movements
- Physical exam: Include vital signs and a full skin exam specifically evaluating all skin surfaces and mucous membranes (eyes, nares, oropharynx, genitals and perianal area). Assess for lymphadenopathy, facial or distal extremity swelling (may be signs of DIHS/DRESS). Assess for pustules or blisters or erosions in addition to areas of “dusky erythema” which may feel painful to palpation. To assess for a positive Nikolsky sign, place a gloved finger tangentially over erythematous skin and apply friction parallel to the skin surface. Nikolsky sign is positive if this results in detached or sloughing epidermis demonstrating poor attachment of the epidermis to the dermis, which is the case in some autoimmune disorders (eg, pemphigus) and SJS/TEN

## Severe Cutaneous Adverse Reactions (SCARs)

Grading	Management
<b>All Grades</b>	In cases of suspected SJS or any mucous membranes involvement, discontinue ICI treatment and monitor closely for improvement regardless of grade
<b>G1: N/A</b>	For the SCARs, there is not a grade 1 category. If lower body surface area is involved with bullae or erosions, there should remain high concern that this reaction will progress to grade 3 or 4
<b>G2:</b> Morbilliform ("maculopapular") exanthem covering 10-30% BSA with systemic symptoms, lymphadenopathy or facial swelling	<ul style="list-style-type: none"> <li>• Hold ICI and monitor patients closely every 3 days with grade 2 irAEs for progression to involvement of greater body surface area and/or mucous membrane involvement</li> <li>• Consider following patients closely using serial photography</li> <li>• Initiate therapy with topical emollients, oral antihistamines and medium-to-high strength topical corticosteroids</li> <li>• Consider initiation of prednisone (or equivalent) 0.5-1 mg/kg tapered over at least 4 weeks</li> </ul>
<b>G3:</b> Skin sloughing covering <10% BSA with mucosal involvement associated signs (eg, erythema, purpura, epidermal detachment and mucous membrane detachment)	<ul style="list-style-type: none"> <li>• Hold ICI therapy and consult with dermatology</li> <li>• Treat skin with topical emollients and other petrolatum emollients, oral antihistamines and high-strength topical corticosteroids. Dimethicone may also be offered as an alternative to petrolatum</li> <li>• Administer IV (methyl)prednisolone (or equivalent) 0.5 -1 mg/kg and convert to oral corticosteroids on response, wean over at least 4 weeks</li> <li>• Admit to burn and/or consult wound services with attention to supportive care, including fluid and electrolyte balance, minimizing insensible water losses and preventing infection</li> <li>• Given the immune mechanism of action of these medicines, use of immune suppression is warranted and should be offered</li> <li>• For mucous membrane involvement of SJS or TEN, appropriate consulting services should be offered to guide management in preventing sequelae from scarring (eg, ophthalmology; ear, nose, and throat; urology; gynecology; etc., as appropriate)</li> </ul>

**G4:** Skin erythema and blistering/sloughing covering  $\geq 10\%$  BSA with associated signs (eg, erythema, purpura, epidermal detachment and mucous membrane detachment) and/or systemic symptoms and concerning associated blood work abnormalities (eg, LFT elevations in the setting of DRESS/DIHS)

- Permanently discontinue ICI
- Admit patient immediately to a burn unit or ICU with consulted dermatology and wound care services. Consider further consultations based on management of mucosal surfaces (eg, ophthalmology; ear, nose, and throat surgery; urology; gynecology; etc.)
- Initiate IV (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering when toxicity resolves to normal
- IVIG or cyclosporine may also be considered in severe or steroid-unresponsive cases
- Consider pain/palliative consultation and/or admission in patients presenting with DRESS manifestations

#### **Additional Considerations:**

The usual prohibition of corticosteroids for Stevens-Johnson Syndrome is not relevant here, as the underlying mechanism is a T-cell immuno-directed toxicity. Adequate suppression is necessary with corticosteroids or other agents and may be prolonged in cases of DRESS/DIHS.

# GASTROINTESTINAL TOXICITIES



## Colitis

**Definition:** A disorder characterized by inflammation of the colon

### Diagnostic Work-up:

#### G2:

- Work-up of blood (CBC, CMP, TSH, ESR, CRP), stool (culture, *Clostridium difficile*, parasite, CMV or other viral etiology, ova and parasite) should be performed
- Consider testing for lactoferrin (for patient stratification to determine who needs more urgent endoscopy) and calprotectin (to follow up on disease activity)
- Screening labs (HIV, hepatitis A and B, and blood quantiferon for TB) to prepare patients to start infliximab should be routinely done in patients at high risk for those infections and appropriately selected patients based on infectious disease expert's evaluation
- Imaging (eg, CT scan of abdomen and pelvis and GI endoscopy with biopsy) should be considered as there is evidence showing the presence of ulceration in the colon can predict steroid refractory course, which may require early infliximab
- Consider repeating endoscopy for patients who do not respond to immunosuppressive agents. Repeating endoscopy for disease monitoring can be considered when clinically indicated and when planning to resume therapy

**G3-4:**

- All the work-up listed for G2 (blood, stool, imaging, and scope with biopsy) should be completed immediately
- Consider repeating endoscopy for patients who do not respond to immunosuppressive agents. Repeating endoscopy for disease monitoring should only be considered when clinically indicated and when planning to resume ICI

**Colitis**

<b>Grading*</b>	<b>Management</b>
<b>All Patients</b>	<p>Counsel all patients to be aware of and inform their healthcare provider immediately if they experience:</p> <ul style="list-style-type: none"> <li>• Abdominal pain, nausea, cramping, blood or mucus in stool or changes in bowel habits</li> <li>• Fever, abdominal distention, obstipation, constipation</li> </ul> <p>For grade 2 or higher, consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to grade 1 or less; concurrent immunosuppressant maintenance therapy should be considered only if clinically indicated in individual cases</p>
<b>G1:</b> Increase of less than 4 stools per day over baseline; mild increase in ostomy output compared to baseline	<ul style="list-style-type: none"> <li>• Continue ICI. Alternatively, ICI may be held temporarily and resumed if toxicity does not exceed grade 1</li> <li>• Monitor for dehydration and recommend dietary changes</li> <li>• Facilitate expedited phone contact with patient/caregiver</li> <li>• May obtain gastroenterology consult for prolonged grade 1 cases</li> </ul>

\* Based on CTCAE for diarrhea, as most often used clinically

**G2:** Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline

- Should hold ICI temporarily until patient's symptoms recover to grade 1. Can consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to grade 1 or less.
- Concurrent immunosuppressant maintenance therapy (<10 mg prednisone equivalent dose) may be offered only if clinically indicated in individual cases
- May also include supportive care with medications such as loperamide if infection has been ruled out
- Should consult with gastroenterology for grade 2 or higher
- Administer corticosteroids, unless diarrhea is transient, starting with initial dose of 1 mg/kg/day prednisone or equivalent.
- When symptoms improve to grade 1 or less, taper corticosteroids over at least 4-6 weeks before resuming treatment, although resuming treatment while on low-dose corticosteroid may also be an option after an evaluation of the risks and benefits
- EGD/colonoscopy, endoscopy evaluation should be highly recommended for cases grade  $\geq 2$  to stratify patients for early treatment of infliximab based on the endoscopic findings and to determine the safety of resuming PD-1, PD-L1 therapy
- Stool inflammatory markers can be considered (lactoferrin and calprotectin) in cases of grade  $\geq 2$  to differentiate functional vs inflammatory diarrhea, and use calprotectin to monitor treatment response if provider prefers
- Repeat colonoscopy is optional for cases grade  $\geq 2$  for disease activity monitoring to achieve complete remission, especially if there is a plan to resume ICI

**G3:** Increase of 7 or more stools per day over baseline, incontinence, hospitalization indicated, severe increase in ostomy output compared to baseline, limiting self-care ADL

- Should consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to grade 1 or less
- Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent)
- Consider hospitalization or outpatient facility for patients with dehydration or electrolyte imbalance
- If symptoms persist  $\geq 3$ -5 days or recur after improvement consider administering IV steroid or non-corticosteroid (eg, infliximab)
- Consider colonoscopy in cases where patients have been on immunosuppression and may be at risk for opportunistic infections as an independent cause for diarrhea (ie, CMV colitis) and for anti-TNF or steroid refractory

**G4:** Life-threatening consequences; urgent intervention indicated

- Permanently discontinue treatment
- Should admit patient when clinically indicated. Patients managed as outpatients should be very closely monitored
- Administer 1-2 mg/kg/day (methyl)prednisolone or equivalent until symptoms improve to grade 1, and then start taper over 4-6 weeks
- Consider early infliximab 5-10 mg/kg if symptoms refractory to steroid within 2-3 days
- Consider lower GI endoscopy if symptoms are refractory despite treatment or there is concern of new infections

#### **Additional Considerations:**

- The use of vedolizumab may be considered in patients refractory to infliximab and/or contraindicated to TNF- $\alpha$  blocker. The decision should be made on an individual basis from gastroenterology and oncology evaluation. This is based on case series showing promising results.<sup>1-3</sup>
- Patients with hepatitis and irAE colitis are rare and management should include permanently discontinuing ICI and offering other immunosuppressant agents that work systemically for both conditions
- Currently, enteritis alone as the cause of diarrhea is uncommon, and requires small bowel biopsy as the evaluation tool. It may be managed similar to colitis, including steroid and/or infliximab, etc.

<sup>1</sup>Hsieh AH, Ferman M, Brown MP, Andrews JM. Vedolizumab: a novel treatment for ipilimumab-induced colitis. *BMJ Case Rep.* 2016; pii:bcr2016216641.

<sup>2</sup>Bergqvist V, Hertervig E, Gedeon P, et al. Vedolizumab treatment for immune checkpoint inhibitor-induced enterocolitis. *Cancer Immunol Immunother.* 2017;66(5):581-592.

<sup>3</sup>Diana P, Mankongppaisarnrung C, Charabaty A. Vedolizumab: a novel approach to the treatment of immune checkpoint inhibitors-induced enterocolitis. Poster P1318. Presented at World Congress of Gastroenterology ACG 2017 Annual Scientific Meeting; October 16, 2017; Orlando, Florida.



## Hepatitis

**Definition:** A disorder characterized by a viral pathologic process involving the liver parenchyma

### Diagnostic Work-up:

- Monitor patient for abnormal liver blood tests: AST, ALT, and bilirubin prior to each infusion and/or weekly if grade 1 LFT elevations. No treatment is recommended for grade 1 LFT abnormality

For grade 2 or higher:

- Work-up for other causes of elevated liver enzymes should be tested, viral hepatitis, alcohol history, iron study, thromboembolic event, liver ultrasound, cross-sectional imaging for potential liver metastasis from primary malignancy. If suspicion for primary autoimmune hepatitis is high, can consider ANAs/ASMAs/ANCAs. For patients with elevated alkaline phosphatase alone, gamma-glutamyl transpeptidase should be tested. For isolated elevation of transaminases, consider checking creatine kinase for other etiologies

## Hepatitis

Grading	Management
All Patients	<p>Counsel all patients to be aware of and inform their healthcare provider immediately if they experience</p> <ul style="list-style-type: none"><li>• Yellowing of skin or whites of the eyes</li><li>• Severe nausea or vomiting</li><li>• Pain on the right side of the abdomen</li><li>• Drowsiness</li><li>• Dark urine (tea colored)</li><li>• Bleeding or bruising more easily than normal</li><li>• Feeling less hungry than usual</li></ul>

<p><b>G1:</b> Asymptomatic (AST or ALT &gt;ULN to 3 X ULN and/or total bilirubin &gt;ULN to 1.5 X ULN)</p>	<ul style="list-style-type: none"> <li>• Continue ICI with close monitoring; consider alternate etiologies</li> <li>• Monitor labs 1 to 2 times weekly</li> <li>• Manage with supportive care for symptom control</li> </ul>
<p><b>G2:</b> Asymptomatic (AST or ALT &gt;3 to ≤5 X ULN and/or total bilirubin &gt;1.5 to ≤3 X ULN)</p>	<ul style="list-style-type: none"> <li>• Hold ICI temporarily and resume if recover to ≤grade 1 on prednisone ≤10 mg/kg/day</li> <li>• For grade 2 hepatic toxicity with symptoms, may administer steroid 0.5-1mg/kg/day prednisone or equivalent if the abnormal elevation persists with significant clinical symptoms in 3-5 days</li> <li>• Increase frequency of monitoring to every 3 days</li> <li>• Infliximab might not be the most appropriate treatment option in the situation of immune-mediated hepatitis given the potential risk of idiosyncratic liver failure (Note: No clear evidence shows the liver toxicity from infliximab in other studies)</li> <li>• In follow-up, may resume ICI treatment followed by taper only when symptoms improve to grade 1 or less and steroid ≤10 mg/day. Taper over at least 1 month</li> <li>• Patients should be advised to stop unnecessary medications and any known hepatotoxic drugs</li> </ul>
<p><b>G3:</b> Symptomatic liver dysfunction, fibrosis by biopsy, compensated cirrhosis, reactivation of chronic hepatitis (AST or ALT 5-20 X ULN and/or total bilirubin 3-10 X ULN)</p>	<ul style="list-style-type: none"> <li>• Permanently discontinue ICI</li> <li>• Immediately start steroid 1-2 mg/kg methylprednisolone or equivalent</li> <li>• If steroid refractory or no improvement after 3 days, consider mycophenolate mofetil or azathioprine (if using azathioprine should test for thiopurine methyltransferase deficiency)</li> <li>• Labs daily/every other day; consider inpatient monitoring for patients with AST/ALT &gt;8 X ULN and/or elevated TB 3 X ULN</li> <li>• Increase frequency of monitoring to every 1 to 2 days</li> <li>• Infliximab might not be the most appropriate treatment option in the situation of immune-mediated hepatitis given the potential risk of liver failure (Note: No clear evidence showing liver toxicity from infliximab in other studies). Alternatives include non-TNF-α agents as systemic immunosuppressants</li> <li>• If no improvement is achieved with corticosteroids, or for patients on combination therapy with a novel agent, with standard chemotherapy, or with targeted therapy, refer to hepatologist for further pathologic evaluation of hepatitis</li> <li>• Steroid taper can be attempted around 4-6 weeks; re-escalate if needed; optimal duration unclear</li> </ul>

**G4:** Decompensated liver function (eg, ascites, coagulopathy, encephalopathy, coma) (AST or ALT >20 X ULN and/or total bilirubin >10 X ULN)

- Permanently discontinue ICI
- Administer 2 mg/kg/day methylprednisolone equivalents
- If steroid refractory or no improvement after 3 days, consider mycophenolate mofetil
- Monitor labs daily; consider inpatient monitoring
- Avoid the use of infliximab in the situation of immune-mediated hepatitis
- Hepatology consult if no improvement was achieved with steroid
- Steroid taper can be attempted around 4-6 weeks when symptoms improve to  $\leq$  grade 1; re-escalate if needed; optimal duration unclear
- Consider transfer to tertiary care facility if necessary



# LUNG TOXICITY

## Pneumonitis

**Definition:** Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging).

No symptomatic, pathologic, or radiographic features are pathognomonic for pneumonitis

### Diagnostic Work-up

- Should include the following: CXR, CT, pulse oximetry
- For grade 2 or higher, may include the following infectious work-up: nasal swab, sputum culture and sensitivity, blood culture and sensitivity, urine culture and sensitivity

## Pneumonitis

Grading	Management
<b>G1:</b> Asymptomatic, confined to one lobe of the lung or less than 25% of lung parenchyma, clinical or diagnostic observations only	<ul style="list-style-type: none"><li>• Hold ICI with radiographic evidence of pneumonitis progression</li><li>• May offer one repeat CT in 3-4 weeks; in patients who have had baseline testing, may offer a repeat spirometry/DLCO in 3-4 weeks</li><li>• May resume ICI with radiographic evidence of improvement or resolution. If no improvement, should treat as grade 2</li><li>• Monitor patients weekly with history and physical examination, pulse oximetry; may also offer CXR</li></ul>
<b>G2:</b> Symptomatic, involves more than one lobe of the lung or 25-50% of lung parenchyma, medical intervention indicate, limiting instrumental ADL	<ul style="list-style-type: none"><li>• Hold ICI until resolution to grade 1 or less</li><li>• Prednisone 1-2 mg/kg/day and taper by 5-10 mg/week over 4-6 weeks</li><li>• Consider bronchoscopy with BAL</li><li>• Consider empiric antibiotics</li><li>• Monitor every 3 days with history and physical examination, pulse oximetry, consider CXR; no clinical improvement after 48-72 hours of prednisone, treat as grade 3</li></ul>

**G3:** Severe symptoms, hospitalization required, involves all lung lobes or > 50% of lung parenchyma, limiting self-care ADL, oxygen indicated

**G4:** Life-threatening respiratory compromise, urgent intervention indicated (intubation)

- Permanently discontinue ICI
- Empiric antibiotics; (methyl)prednisolone IV 1-2 mg/kg/day; no improvement after 48 hours, may add infliximab 5 mg/kg or mycophenolate mofetil IV 1 g twice a day or IVIG for 5 days or cyclophosphamide; taper corticosteroids over 4-6 weeks
- Pulmonary and infectious disease consults if necessary
- Bronchoscopy with BAL +/- transbronchial biopsy
- Patients should be hospitalized for further management

#### **Additional Considerations:**

- GI and *Pneumocystis* prophylaxis with PPI and sulfamethoxazole/trimethoprim may be offered to patients on prolonged steroid use (>12 weeks), according to institutional guidelines
- Consider calcium and vitamin D supplementation with prolonged steroid use
- The role of prophylactic fluconazole with prolonged steroid use (>12 weeks) remains unclear and physicians should proceed according to institutional guidelines
- Bronchoscopy + biopsy; if clinical picture is consistent with pneumonitis, no need for biopsy



## ENDOCRINE TOXICITIES

Counsel patients to inform their healthcare provider immediately if they experience any changes in their health since their last visit, especially any of the following:

- Headaches that will not go away or unusual headache patterns
- Vision changes
- Rapid heartbeat
- Increased sweating
- Extreme tiredness or weakness
- Muscle aches
- Weight gain or weight loss
- Dizziness or fainting
- Feeling more hungry or thirsty than usual
- Hair loss
- Changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness
- Feeling cold
- Constipation
- Voice gets deeper
- Urinating more often than usual
- Nausea or vomiting
- Abdominal pain

## Primary Hypothyroidism

**Definition:** Elevated TSH, normal or low FT4

### Diagnostic Work-up:

TSH and FT4 every 4-6 weeks as part of routine clinical monitoring on therapy or for case detection in symptomatic patients

## Primary Hypothyroidism

Grading	Management
<b>G1:</b> TSH <10 mIU/L and asymptomatic	Should continue ICI with close follow-up and monitoring of TSH, FT4
<b>G2:</b> Moderate symptoms; able to perform ADL; TSH persistently >10 mIU/L	<ul style="list-style-type: none"><li>• May hold ICI until symptoms resolve to baseline</li><li>• Consider endocrine consultation</li><li>• Prescribe thyroid hormone supplementation in symptomatic patients with any degree of TSH elevation or in asymptomatic patients with TSH levels that persist &gt;10 mIU/L (measured 4 weeks apart)</li><li>• Monitor TSH every 6-8 weeks while titrating hormone replacement to normal TSH</li><li>• FT4 can be used in the short term (2 weeks) to ensure adequacy of therapy in those with frank hypothyroidism where the FT4 was initially low</li><li>• Once adequately treated, should monitor thyroid function (at least TSH) every 6 weeks while on active ICI therapy or as needed for symptoms to ensure appropriate replacement. Repeat testing annually or as indicated by symptoms once stable</li></ul>
<b>G3-4:</b> Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	<ul style="list-style-type: none"><li>• Hold ICI until symptoms resolve to baseline with appropriate supplementation</li><li>• Endocrine consultation</li><li>• May admit for IV therapy if signs of myxedema (bradycardia, hypothermia)</li><li>• Thyroid supplementation and reassessment as in grade 2</li></ul>

### **Additional Considerations**

- For patients without risk factors, full replacement can be estimated with an ideal body weight-based dose of approximately 1.6 mcg/kg/day
- For elderly or fragile patients with multiple comorbidities, consider titrating up from low dose, starting at 25-50 mcg
- Extreme elevations of TSH can be seen in the recovery phase of thyroiditis and can be watched in asymptomatic patients to determine whether there is recovery to normal within 3-4 weeks
- Under guidance of endocrinology, consider tapering hormone replacement and retesting in patients with a history of thyroiditis (initial thyrotoxic phase)
- Adrenal dysfunction, if present, must always be replaced before thyroid hormone therapy is initiated

## **Hyperthyroidism**

**Definition:** Suppressed TSH and high normal or elevated FT4 and/or T3

### **Diagnostic Work-up:**

- Monitor TSH, free T4 every 4-6 weeks from the start of therapy or as needed for case detection in symptomatic patients
- Consider TSH receptor antibodies if there are clinical features and suspicion of Grave's disease (eg, ophthalmopathy)
- Close monitoring of thyroid function every 2-3 weeks after diagnosis to catch transition to hypothyroidism in patients with thyroiditis and hyperthyroidism

## Hyperthyroidism

Grading	Management
<p><b>G1:</b> Asymptomatic or mild symptoms</p>	<ul style="list-style-type: none"> <li>• Can continue ICI with close follow-up and monitoring of TSH, FT4 every 2-3 weeks until it is clear whether there will be persistent hyperthyroidism (see below) or hypothyroidism (see page 24)</li> </ul>
<p><b>G2:</b> Moderate symptoms, able to perform ADL</p>	<ul style="list-style-type: none"> <li>• Consider holding ICI until symptoms return to baseline</li> <li>• Consider endocrine consultation</li> <li>• Beta-blocker (eg, atenolol or propranolol) for symptomatic relief</li> <li>• Hydration and supportive care</li> <li>• Corticosteroids are not usually required to shorten duration</li> <li>• For persistent hyperthyroidism (&gt;6 weeks) or clinical suspicion, work-up for Graves disease (TSI or TRAb) and consider thionamide (methimazole or PTU)</li> <li>• Refer to endocrinology for Graves disease</li> </ul>
<p><b>G3-4:</b> Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL</p>	<ul style="list-style-type: none"> <li>• Hold ICI until symptoms resolve to baseline with appropriate therapy</li> <li>• Endocrine consultation</li> <li>• Beta-blocker (eg, atenolol or propranolol) for symptomatic relief</li> <li>• For severe symptoms or concern for thyroid storm, hospitalize patient and initiate prednisone 1-2 mg/kg/day or equivalent tapered over 1-2 weeks. Consider also use of SSKI or thionamide (methimazole or PTU)</li> </ul>

### Additional Considerations:

- Thyroiditis is transient and resolves in a couple of weeks to primary hypothyroidism or normal. Hypothyroidism can be treated as above
- Graves disease is generally persistent and is due to increased thyroid hormone production that can be treated with anti-thyroid medical therapy
- Physical exam findings of ophthalmopathy or thyroid bruit are diagnostic of Graves and should prompt early endocrine referral

## Primary Adrenal Insufficiency

**Definition:** Adrenal gland failure leading to low morning cortisol, high morning ACTH, as well as hyponatremia and hyperkalemia with orthostasis and volume depletion due to loss of aldosterone

### Diagnostic Work-up for patients in whom adrenal insufficiency is suspected:

- Evaluate ACTH (AM), cortisol level (AM)
- Basic metabolic panel (Na, K, CO<sub>2</sub>, glucose)
- Consider ACTH stimulation test for indeterminate results

If primary adrenal insufficiency (high ACTH, low cortisol) is found biochemically:

- Evaluate for precipitating cause of crisis such as infection
- Adrenal CT for metastasis/hemorrhage

## Primary Adrenal Insufficiency

Grading	Management
<b>G1:</b> Asymptomatic or mild symptoms	<ul style="list-style-type: none"><li>• Consider holding ICI until patient is stabilized on replacement hormone.</li><li>• Endocrine consultation</li><li>• Replacement therapy with prednisone (5-10 mg daily) or hydrocortisone (10-20 mg orally every morning, 5-10 mg orally in early afternoon)</li><li>• May require fludrocortisone (0.1 mg/day) for mineralocorticoid replacement in primary adrenal insufficiency</li><li>• Titrate dose up or down as symptoms dictate</li></ul>
<b>G2:</b> Moderate symptoms, able to perform ADL	<ul style="list-style-type: none"><li>• Consider holding ICI until patient is stabilized on replacement hormone.</li><li>• Endocrine consultation</li><li>• Initiate outpatient treatment at 2-3 times maintenance (eg, if prednisone, 20 mg daily; if hydrocortisone 20-30 mg in the morning and 10-20 mg in the afternoon) to manage acute symptoms</li><li>• Taper stress-dose corticosteroids down to maintenance doses over 5-10 days</li><li>• Maintenance therapy as in grade 1</li></ul>

**G3-4:** Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL

- Hold ICI until patient is stabilized on replacement hormone
- Endocrine consultation
- See in clinic or, if after hours, make an emergency department referral for normal saline (at least 2 L) and IV stress-dose corticosteroids on presentation (hydrocortisone 100 mg or dexamethasone 4 mg (if the diagnosis is not clear and stimulation testing will be needed))
- Taper stress-dose corticosteroids down to maintenance doses over 7-14 days after discharge
- Maintenance therapy as in grade 1

**Additional Considerations:**

- Primary and secondary adrenal insufficiency can be distinguished by the relationship between ACTH and cortisol. If the ACTH is low with low cortisol, then management is as per hypophysitis
- Patients on corticosteroids for management of other conditions, will have low morning cortisol as a result of iatrogenic, secondary adrenal insufficiency. ACTH will also be low in these patients. A diagnosis of adrenal insufficiency is challenging to make in these situations (see section on hypophysitis)
- Emergent therapy for someone with suspected adrenal insufficiency is best done with dexamethasone as a stimulation test can still be performed. If the diagnosis is already confirmed, can use hydrocortisone 100 mg
- All patients need education on stress dosing and a medical alert bracelet for adrenal insufficiency to trigger stress-dose corticosteroids by EMS
- Endocrine consultation prior to surgery or any procedure for stress-dose planning

## Hypophysitis

**Definition:** inflammation of the pituitary with varying impacts on hormone function. Most commonly presenting with central adrenal insufficiency. May also have central hypothyroidism, diabetes insipidus and hypogonadism

### Diagnostic Work-up:

Diagnosis: Low ACTH with a low cortisol. Low or normal TSH with a low FT4. Hyponatremia and volume depletion with diabetes insipidus. Low testosterone or estradiol with low LH and FSH

Testing:

- Evaluate ACTH, cortisol (AM), TSH, FT4, electrolytes
- Consider evaluating LH, FSH and testosterone levels in males or estrogen in premenopausal females with fatigue, loss of libido and mood changes
- Consider MRI of the brain with or without contrast with pituitary/sellar cuts in patients with multiple endocrine abnormalities +/- new severe headaches or complaints of vision changes

## Hypophysitis

Grading	Management
<b>G1:</b> Asymptomatic or mild symptoms	<ul style="list-style-type: none"><li>• Consider holding ICI until patient is stabilized on replacement hormones</li><li>• Hormonal supplementation as needed, using dosing as above for primary hypothyroidism and adrenal insufficiency (eg, hydrocortisone 10-20 mg orally in the morning, 5-10 mg orally in early afternoon; levothyroxine by weight)</li><li>• Testosterone or estrogen therapy as needed in those without contraindications</li><li>• Endocrine consultation</li><li>• Always start corticosteroids several days before thyroid hormone to prevent precipitating adrenal crisis</li><li>• Follow FT4 for thyroid hormone replacement titration (TSH is not accurate)</li></ul>
<b>G2:</b> Moderate symptoms, able to perform ADL	<ul style="list-style-type: none"><li>• Consider holding ICI until patient is stabilized on replacement hormones</li><li>• Endocrine consultation</li><li>• Hormonal supplementation as in grade 1</li></ul>

**G3-4:** Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL

- Hold ICI until patient is stabilized on replacement hormones.
- Endocrine consultation
- Hormonal supplementation as in grade 1
- Consider initial pulse dose therapy with prednisone 1-2 mg/kg oral daily (or equivalent) tapered over at least 1-2 weeks

#### **Additional Considerations:**

- Please be aware of the need to start corticosteroids first when planning hormone replacement therapy for multiple deficiencies
- All patients need instruction on doubling doses for illness (stress dosing) and a medical alert bracelet for adrenal insufficiency to trigger stress-dose corticosteroids by EMS
- Steroid use can cause isolated central adrenal insufficiency
- Work-up cannot be done with a simple AM cortisol in a patient on corticosteroids for other conditions
- Laboratory confirmation of adrenal insufficiency should not be attempted until treatment with corticosteroids for other disease is ready to be discontinued
- For long term exposure, consult endocrinology for recovery and weaning protocol using hydrocortisone

## **Diabetes**

**Definition:** T2DM is a combination of insulin resistance and insufficiency that may require oral or insulin therapy. It may be new onset or exacerbated during therapy for non-immunologic reasons such as steroid exposure.

Autoimmune T1DM results from islet cell destruction and is often acute onset, with ketosis and an insulin requirement.

#### **Diagnostic Work-up:**

- Monitor patients for hyperglycemia or other signs and symptoms of new or worsening DM, including measuring glucose at baseline and with each treatment cycle during induction for 12 weeks, then every 3-6 weeks thereafter. To guide the work-up in new onset hyperglycemia, clinicians should consider a patient's medical background, exposure history, and risk factors for each subtype of DM
- Laboratory evaluation in suspected T1DM should include testing for ketosis in urine and an assessment of the anion gap on a metabolic panel. Anti-glutamic acid decarboxylase, anti-islet cell or anti-insulin antibodies are highly specific for autoimmune diabetes. Insulin and C-peptide levels can also assist in the diagnosis

## Diabetes

Grading	Management
<p><b>G1:</b> Asymptomatic or mild symptoms; fasting glucose value &gt;ULN (160 mg/dL); no evidence of ketosis or laboratory evidence of T1DM at any glucose level</p>	<ul style="list-style-type: none"> <li>• Can continue ICI with close clinical follow-up and laboratory evaluation</li> <li>• May initiate oral therapy for those with new-onset T2DM</li> <li>• Screen for T1DM if appropriate (eg, acute onset with prior normal values or clinical concern for ketosis)</li> </ul>
<p><b>G2:</b> Moderate symptoms, able to perform ADL; fasting glucose value &gt;160-250 mg/dL; ketosis or evidence of T1DM at any glucose level</p>	<ul style="list-style-type: none"> <li>• May hold ICI until glucose control is obtained</li> <li>• Titrate oral therapy or add insulin for worsening control in T2DM</li> <li>• Should administer insulin for T1DM (or as default therapy if there is confusion about type)</li> <li>• Urgent endocrine consultation for any patient with T1DM. In the absence of endocrinology, internal medicine may suffice</li> <li>• Consider admission for T1DM if early outpatient evaluation is not available or signs of ketoacidosis are present</li> </ul>
<p><b>G3-4:</b> Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL</p> <p>G3: &gt;250 - 500 mg/dL</p> <p>G4: &gt;500 mg/dL</p>	<ul style="list-style-type: none"> <li>• Hold ICI until glucose control is obtained on therapy with reduction of toxicity to grade 1 or less</li> <li>• Urgent endocrine consultation for all patients</li> <li>• Initiate insulin therapy for all patients</li> </ul> <p>Admit for inpatient management:</p> <ul style="list-style-type: none"> <li>• Concerns for developing DKA</li> <li>• Symptomatic patients regardless of diabetes type</li> <li>• New onset T1DM unable to see endocrinology</li> </ul>

**Additional Considerations:**

- Insulin therapy can be used as the default in any case with hyperglycemia
- Long-acting therapy alone is not usually sufficient for T1DM, where half of daily requirements are usually given in divided doses as prandial coverage and half as long-acting
- Insulin doses will be lower in T1DM because of preserved sensitivity (total daily requirement can be estimated at 0.3-0.4 units/kg/day)
- In T2DM, sliding scale coverage with meals over a few days provides data to estimate a patient's daily requirements and can be used to more rapidly titrate basal needs



# MUSCULOSKELETAL TOXICITIES

## Inflammatory Arthritis

**Definition:** A disorder characterized by inflammation of the joints

**Clinical Symptoms:** Joint pain accompanied by joint swelling, inflammatory symptoms such as stiffness after inactivity or in the morning, lasting more than 30 minutes to 1 hour. Improvement of symptoms with NSAIDs or corticosteroids, but not with opioids or other pain meds may also be suggestive of inflammatory arthritis

### Diagnostic Work-up:

#### G1:

- Complete rheumatologic history and examination of all peripheral joints for tenderness, swelling and range of motion; examination of the spine
- Consider plain X-ray/imaging to exclude metastases and evaluate joint damage (erosions) if appropriate
- Consider autoimmune blood panel including ANA, RF, and anti-CCP and anti-inflammatory markers (ESR and CRP) if symptoms persist. If symptoms are suggestive of reactive arthritis or affect the spine, consider HLA B27 testing

#### G2:

- Complete history and examination as above; laboratory tests as above
- Consider US +/- MRI of affected joints if clinically indicated (eg, persistent arthritis unresponsive to treatment, suspicion for differential diagnoses such as metastatic lesions or septic arthritis)
- Consider early referral to a rheumatologist, if there is joint swelling (synovitis) or if symptoms persists >4 weeks

#### G3-4:

- As for grade 2
- Seek rheumatologist advice and review

### Monitoring:

Patients with inflammatory arthritis should be monitored with serial rheumatologic examinations, including inflammatory markers, every 4-6 weeks after treatment is instituted

## Inflammatory Arthritis

Grading	Management
<b>All Grades</b>	Clinicians should follow reports of new joint pain to determine whether inflammatory arthritis is present. Question whether symptom new since receiving ICI
<p><b>G1:</b> Mild pain with inflammation, erythema, or joint swelling</p> <p><b>G2:</b> Moderate pain associated with signs of inflammation, erythema, or joint swelling, limiting instrumental ADL</p>	<ul style="list-style-type: none"> <li>• Continue ICI</li> <li>• Initiate analgesia with acetaminophen and/or NSAIDs</li> <li>• Hold ICI and resume upon symptom control and on prednisone <math>\leq 10</math> mg/day</li> <li>• Escalate analgesia and consider higher doses of NSAIDs as needed</li> <li>• If inadequately controlled, initiate prednisone or prednisolone 10-20 mg/day or equivalent for 4-6 weeks</li> <li>• If improvement, slow taper according to response during the next 4-6 weeks. If no improvement after initial 4-6 weeks treat as grade 3</li> <li>• If unable to lower corticosteroid dose to <math>&lt; 10</math> mg/day after 3 months, consider DMARD</li> <li>• Consider intra-articular steroid injections for large joints</li> <li>• Referral to rheumatology</li> </ul>
<p><b>G3-4:</b> Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self-care ADL</p>	<ul style="list-style-type: none"> <li>• Hold ICI temporarily and may resume in consultation with rheumatology, if recover to grade 1 or less</li> <li>• Initiate oral prednisone 0.5-1 mg/kg</li> <li>• If failure of improvement after 4 weeks or worsening in meantime, consider synthetic or biologic DMARD</li> </ul> <p><i>Synthetic: methotrexate, leflunomide</i></p> <p><i>Biologic: consider anticytokine therapy such as TNF-<math>\alpha</math> or IL-6 receptor inhibitors. (Note: as caution, IL-6 inhibition can cause intestinal perforation; while this is extremely rare, it should not be used in patients with colitis.)</i></p> <ul style="list-style-type: none"> <li>• Test for viral hepatitis B, C and latent/active TB test prior to DMARD treatment</li> <li>• Referral to rheumatology</li> </ul>

**Additional Considerations:**

- Early recognition is critical to avoid erosive joint damage
- Corticosteroids can be used as part of initial therapy in inflammatory arthritis, but due to likely prolonged treatment requirements, physicians should consider starting steroid-sparing agents earlier than one would with other irAEs
- Oligoarthritis can be treated early on with intra-articular corticosteroids, consider early referral
- Consider PCP prophylaxis for patients treated with high dose of corticosteroids for longer than 12 weeks, as per local guidelines

## Myositis

**Definition:** A disorder characterized by muscle inflammation with weakness and elevated muscle enzymes (CK). Muscle pain can be present in severe cases. Can be life-threatening if respiratory muscles or myocardium are involved

**Diagnostic Work-up:**

- Complete rheumatological and neurological history regarding differential diagnosis and rheumatological and neurological examination including muscle strength, and examination of the skin for findings suggestive of dermatomyositis. Muscle weakness is more typical of myositis than pain. Consider pre-existing conditions that can cause similar symptoms
- Blood testing to evaluate muscle inflammation
- Creatine kinase (CK), transaminases (AST, ALT), LDH and aldolase can also be elevated
- Troponin to evaluate myocardial involvement, and other cardiac testing such as echocardiogram as needed
- Inflammatory markers (ESR and CRP)
- Consider EMG, MRI, and/or biopsy on an individual basis when diagnosis is uncertain, and overlap with neurologic syndromes such as myasthenia gravis is suspected.
- Consider paraneoplastic autoantibody testing for myositis and neurological conditions such as myasthenia gravis

**Monitoring:** CK, ESR, CRP

**G1:** Complete examination and laboratory work-up as above

**G2:** Complete history and examination as above; autoimmune myositis blood panel; EMG, MRI imaging of affected joints; early referral to a rheumatologist or neurologist

**G3-4:** As for grade 2

Urgent referral to a rheumatologist or neurologist

## Myositis

Grading	Management
<p><b>G1:</b> Mild weakness with or without pain</p>	<ul style="list-style-type: none"> <li>• Continue ICI</li> <li>• If CK is elevated and patient has muscle weakness, may offer oral corticosteroids, and treat as grade 2</li> <li>• Offer analgesia with acetaminophen or NSAIDs if there are no contraindications</li> </ul>
<p><b>G2:</b> Moderate weakness with or without pain, limiting age-appropriate instrumental ADL</p>	<ul style="list-style-type: none"> <li>• Hold ICI temporarily and may resume upon symptom control, if CK is normal and prednisone dose &lt;10 mg; if worsens, treat as per grade 3</li> <li>• NSAIDs as needed</li> <li>• Referral to rheumatologist or neurologist</li> <li>• If CK is elevated (3 times or more), initiate prednisone or equivalent at 0.5-1 mg/kg</li> <li>• May require permanent discontinuation of ICI in most cases with grade 2 symptoms and objective findings (elevated enzymes, abnormal EMG, abnormal muscle MRI or biopsy)</li> </ul>
<p><b>G3-4:</b> Severe weakness with or without pain; limiting self care ADL</p>	<ul style="list-style-type: none"> <li>• Hold ICI until grade 1 or less off immune suppression and permanently discontinue if any evidence of myocardial involvement</li> <li>• Consider hospitalization for severe weakness</li> <li>• Referral to rheumatologist or neurologist</li> <li>• Initiate prednisone 1 mg/kg or equivalent. Consider 1-2 mg/kg of methylprednisolone IV or higher-dose bolus if severe compromise (weakness severely limiting mobility, cardiac, respiratory, dysphagia)</li> <li>• Consider plasmapheresis</li> <li>• Consider IVIG therapy</li> <li>• Consider other immunosuppressant therapy such as methotrexate, azathioprine, or mycophenolate mofetil if symptoms and CK levels do not improve or worsen after 4-6 weeks. Rituximab is used in primary myositis but caution is advised given its long biological duration</li> </ul>

### Additional Considerations:

Caution is advised with rechallenging

## Polymyalgia-like Syndrome

**Definition:** Characterized by marked pain and stiffness in proximal upper and/or lower extremities, and no signs of true muscle inflammation such as CK elevation or EMG findings of myositis. No true muscle weakness, difficulty in active motion related to pain

### **Diagnostic Work-up:**

#### **G1:**

- Complete rheumatologic history regarding differential diagnosis and examination of all joints and skin
- Check for symptoms of temporal arteritis, such as headache or visual disturbances; refer to ophthalmologist if present, and consider temporal artery biopsy
- ANA, RF, anti-CCP
- CK to evaluate differential diagnosis of myositis
- Inflammatory markers (ESR, CRP)
- Monitoring: ESR, CRP

**G2:** Complete history and examination as above; autoimmune tests as required for differential diagnosis; early referral to a rheumatologist

**G3-4:** As for grade 2; seek rheumatologist advice and review

## Polymyalgia-like Syndrome

Grading	Management
<b>G1:</b> Mild stiffness and pain	<ul style="list-style-type: none"><li>• Continue ICI</li><li>• Initiate analgesia with acetaminophen and/or NSAIDs if there are no contraindications</li></ul>
<b>G2:</b> Moderate stiffness and pain ; limiting age-appropriate instrumental ADL	<ul style="list-style-type: none"><li>• Consider holding ICI and resuming upon symptom control, prednisolone &lt;10 mg; if worsens, treat as per grade 3</li><li>• Initiate prednisone 20 mg/day or equivalent. If symptoms improve, start to taper dose after 3-4 weeks.</li><li>• If no improvement or need for higher dosages after 4 weeks, escalate to grade 3</li><li>• Consider referral to rheumatology</li></ul>
<b>G3-4:</b> Severe stiffness and pain; limiting self care ADL	<ul style="list-style-type: none"><li>• Hold ICI and may resume, in consultation with rheumatology, if recover to grade 1 or less; however, note that cases of toxicity returning upon rechallenge have been reported.</li><li>• Referral to rheumatology</li><li>• Should initiate prednisone 20 mg/day or equivalent. If no improvement or need for higher dosages for prolonged time, may offer a steroid sparing agent such as methotrexate or IL-6 inhibition with tocilizumab. Note: As caution, IL-6 inhibition can cause intestinal perforation; while this is extremely rare, it should not be used in patients with colitis or GI metastases</li><li>• Consider admission for pain control</li></ul>



# RENAL TOXICITIES

## Nephritis and Renal Dysfunction

### Diagnosis and Monitoring:

- For any suspected immune-mediated adverse reactions, exclude other causes
- Monitor patients for elevated serum creatinine prior to every dose
- Routine urinalysis is not necessary, other than to rule out UTIs, etc. Nephrology may consider further
- If no potential alternative cause of AKI identified, then one should forego biopsy and proceed directly with immunosuppressive therapy
- Swift treatment of autoimmune component important

## Nephritis

**Definition:** Inflammation of the kidney affecting the structure

## Nephritis

Grading	Management
<b>G1:</b> Creatinine level increase of >0.3 mg/dL; creatinine 1.5-2 X over baseline	<ul style="list-style-type: none"><li>• Consider temporarily holding ICI, pending consideration of potential alternative etiologies (recent IV contrast, medications, fluid status) and baseline renal function. A change that is still &lt;1.5 ULN could be meaningful</li></ul>
<b>G2:</b> Creatinine 2-3 X above baseline	<ul style="list-style-type: none"><li>• Hold ICI temporarily</li><li>• Consult nephrology</li><li>• Evaluate for other causes (recent IV contrast, medications, fluid status etc.) If other etiologies ruled out, administer 0.5 to 1 mg/kg/day prednisone equivalents</li><li>• If worsening or no improvement: 1 to 2 mg/kg/day prednisone equivalents and permanently discontinue treatment</li><li>• If improved to grade 1 or less, taper corticosteroids over 4-6 weeks</li><li>• If no recurrence of chronic renal insufficiency, discuss resumption of ICI with patient after taking into account the risks and benefits.</li></ul>
<b>G3:</b> Creatinine >3 X baseline or >4.0 mg/dL; hospitalization indicated <b>G4:</b> Life-threatening consequences; dialysis indicated	<ul style="list-style-type: none"><li>• Permanently discontinue ICI</li><li>• Consult nephrology</li><li>• Evaluate for other causes (recent IV contrast, medications, fluid status etc.)</li><li>• Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent)</li></ul>

**Additional Considerations:** Monitor creatinine weekly; reflex kidney biopsy should be discouraged until steroid treatment has been attempted.

## Symptomatic Nephritis – Follow Up

Grading	Management
<b>G1</b>	If improved to baseline, resume routine creatinine monitoring
<b>G2</b>	If improved to grade 1: <ul style="list-style-type: none"><li>• Taper corticosteroids over at least 3 weeks before resuming treatment with routine creatinine monitoring</li><li>• If elevations persist &gt; 7 days or worsen and no other cause found, treat as grade 3</li></ul>
<b>G3</b>	If improved to grade 1: <ul style="list-style-type: none"><li>• Taper corticosteroids over at least 4 weeks</li><li>• If elevations persist &gt; 3-5 days or worsen, consider additional immunosuppression (eg, mycophenolate)</li></ul>
<b>G4</b>	If improved to grade 1: <ul style="list-style-type: none"><li>• Taper corticosteroids over at least 4 weeks</li><li>• If elevations persist &gt; 2-3 days or worsen, consider additional immunosuppression (eg, mycophenolate)</li></ul>



# NERVOUS SYSTEM TOXICITIES

## Myasthenia Gravis

**Definition:** Fatigable or fluctuating muscle weakness, generally more proximal than distal. Frequently has ocular and/or bulbar involvement (ptosis, extraocular movement abnormalities resulting in double vision, dysphagia, dysarthria, facial muscle weakness). May have neck and/or respiratory muscle weakness. Note: May occur with myositis and/or myocarditis. Respiratory symptoms may require evaluation to rule out pneumonitis, myocarditis. Miller Fisher variant of Guillain Barre syndrome (ophthalmoparesis) and the oculobulbar myositis (ptosis, ophthalmoparesis, dysphagia, neck and respiratory weakness) with ICI may have overlapping symptoms.

### Diagnostic Work-up:

- Acetylcholine receptor (AChR) and anti-striated muscle antibodies in blood. If AChR antibodies are negative, consider muscle specific kinase (MuSK) and lipoprotein related 4 (LPR4) antibodies in blood.
- Pulmonary function assessment with NIF (negative inspiratory force) and VC (vital capacity)
- CPK, aldolase, ESR, CRP for possible concurrent myositis
- Consider MRI of brain and/or spine depending on symptoms, to rule out CNS involvement by disease or alternate diagnosis
- If respiratory insufficiency or elevated CPK, troponin T, perform cardiac exam, ECG and TTE for possible concomitant myocarditis
- Neurological consultation
- Electrodiagnostic studies, including neuromuscular junction testing with repetitive stimulation and/or jitter studies, NCS to exclude neuropathy, and needle EMG to evaluate for myositis.

## Myasthenia Gravis

Grading	Management
<b>All Grades</b>	All grades warrant Work-up and intervention given potential for progressive myasthenia gravis to lead to respiratory compromise
<b>No G1</b>	
<p><b>G2:</b> Some symptoms interfering with ADL</p> <p>MGFA severity class I (ocular symptoms and findings only) and MGFA severity class II (mild generalized weakness)</p>	<ul style="list-style-type: none"> <li>• Hold ICI and may resume in grade 2 patients (MGFA 1 and 2) only if symptoms resolve</li> <li>• Should consult neurology</li> <li>• Pyridostigmine starting at 30 mg orally three times a day and gradually increase to maximum of 120 mg orally four times a day as tolerated and based on symptoms</li> <li>• Administer corticosteroids (prednisone 1-1.5mg/kg orally daily) if symptoms grade 2; wean based on symptom improvement</li> </ul>
<p><b>G3-4:</b> Limiting self-care and aids warranted, weakness limiting walking, ANY dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms, or MGFA severity class 3-4 moderate to severe generalized weakness to myasthenic crisis</p>	<ul style="list-style-type: none"> <li>• Permanently discontinue ICI</li> <li>• Admit patient, may need ICU-level monitoring.</li> <li>• Neurology consult</li> <li>• Continue steroids and initiate IVIG 2 g/kg IV over 5 days (0.4 g/kg/day) or plasmapheresis for 5 days</li> <li>• Frequent pulmonary function assessment</li> <li>• Daily neurological review</li> </ul>

### Additional Considerations:

- Avoid medications that can worsen myasthenia: beta-blockers, IV magnesium, fluoroquinolones, aminoglycosides and macrolides
- Initially a 5-day course of plasmapheresis or a 2 g/kg course of IVIG over 5 days
- 1-2 mg/kg methylprednisolone daily, wean based on symptom improvement
- Pyridostigmine, wean based on improvement.
- ICI-associated myasthenia gravis may be monophasic, and additional steroid sparing agents may not be required

## Guillain-Barré Syndrome (GBS)

**Definition:** Progressive, most often symmetrical muscle weakness with absent or reduced deep tendon reflexes. Often starts with sensory symptoms/neuropathic pain localized to lower back and thighs. May involve extremities (typically ascending weakness but not always), facial, respiratory and bulbar & oculomotor nerves. May have dysregulation of autonomic nerves

### Diagnostic Work-up:

- Neurologic consultation
- MRI of spine with or without contrast (rule out compressive lesion and evaluate for nerve root enhancement/thickening)
- Lumbar puncture: CSF typically has elevated protein and often elevated WBC as well, though this is not typically seen in classical Guillain-Barre syndrome; cytology (should be sent with any CSF sample from a patient with cancer)
- Serum antiganglioside antibody tests for Guillain-Barré syndrome and its subtypes (eg, anti-GQ1b for Miller Fisher variant associated with ataxia and ophthalmoplegia)
- Electrodiagnostic studies to evaluate polyneuropathy
- Pulmonary function testing (NIF/VC)
- Frequent neurochecks

## Guillain-Barré Syndrome

Grading	Management
<b>All grades</b>	Warrant work-up and intervention given potential for progressive GBS to lead to respiratory compromise. Note: There is no grade 1 toxicity
<b>G1:</b> Mild: None	NA
<p><b>G2:</b> Moderate: Some interference with ADL, symptoms concerning to patient</p> <p><b>G3-4:</b> Severe: Limiting self-care and aids warranted, weakness limiting walking, ANY dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms</p>	<ul style="list-style-type: none"> <li>• Discontinue ICI</li> <li>• Admission to inpatient unit with capability of rapid transfer to ICU-level monitoring</li> <li>• Start IVIG (0.4 g/kg/day for 5 days for a total dose of 2 g/kg) or plasmapheresis.</li> <li>• Corticosteroids are usually not recommended for idiopathic GBS, however in ICI-related forms, a trial is reasonable (methylprednisolone 2-4 mg/kg/day), followed by slow steroid taper.</li> <li>• Pulse steroid dosing (methylprednisolone 1 gram daily for 5 days) may also be considered for grade 3-4 along with IVIG or plasmapheresis</li> <li>• Frequent neurochecks and pulmonary function monitoring</li> <li>• Monitor for concurrent autonomic dysfunction</li> <li>• Nonopioid management of neuropathic pain</li> <li>• Treatment of constipation/ileus</li> </ul>

### Additional Considerations:

- Slow prednisone taper after steroid pulse plus IVIG or plasmapheresis
- May require repeat IVIG courses
- Caution with rechallenging for severe cases

## Peripheral Neuropathy

**Definition:** Can present as asymmetric or symmetric sensory, motor, or sensory-motor deficit. Focal mononeuropathies including cranial neuropathies (eg, facial neuropathies/Bell palsy) may be present. Numbness and paresthesias may be painful or painless. Hypo- or areflexia or sensory ataxia may be present

### Diagnostic Work-up:

#### G1:

- Screen for reversible neuropathy causes: diabetic screen, B12, folate, TSH, HIV, consider serum protein electrophoresis, and other vasculitic & autoimmune screen
- Neurologic consultation
- Consider MRI of spine with or without contrast

#### G2: In addition to above:

- MRI of spine advised/MRI of brain if cranial nerve
- Consider EMG/NCS
- Consider neurology consultation

#### G3-4: Go to GBS algorithm

## Peripheral Neuropathy

Grading	Management
<p><b>G1:</b> Mild: No interference with function and symptoms not concerning to patient. Note: Any cranial nerve problem should be managed as moderate</p>	<ul style="list-style-type: none"><li>• Low threshold to hold ICI and monitor symptoms for a week</li><li>• If to continue, monitor very closely for any symptom progression</li></ul>
<p><b>G2:</b> Moderate: Some interference with ADL, symptoms concerning to patient (ie, pain but no weakness or gait limitation)</p>	<ul style="list-style-type: none"><li>• Hold ICI and resume once return to grade 1</li><li>• Initial observation OR initiate prednisone 0.5-1 mg/kg (if progressing from mild)</li><li>• Gabapentin, pregabalin, or duloxetine for pain</li></ul>
<p><b>G3-4:</b> Severe: Limiting self-care and aids warranted, weakness limiting walking or respiratory problems (ie, leg weakness, foot drop, rapidly ascending sensory changes). Severe may be GBS and should be managed as such</p>	<ul style="list-style-type: none"><li>• Permanently discontinue ICI</li><li>• Admit patient</li><li>• Neurologic consultation</li><li>• Initiate IV methylprednisolone 2-4 mg/kg and proceed as per GBS management.</li></ul>

## Autonomic Neuropathy

**Definition:** Nerves that control involuntary bodily functions are damaged. This may affect blood pressure, temperature control, digestion, bladder function and sexual function. A case of severe enteric neuropathy with ICI has been reported

Can present with GI difficulties such as new severe constipation, nausea; urinary problems, sexual difficulties, sweating abnormalities, sluggish pupil reaction and orthostatic hypertension

### Diagnostic Work-up:

An evaluation by neurologist or relevant specialist depending on organ system, with testing which may include:

- Screen for other causes of autonomic dysfunction: diabetic screen, adrenal insufficiency, HIV, paraproteinemia, amyloidosis, botulism; consider chronic diseases such as Parkinson's and other autoimmune screening
- Orthostatic vital signs
- Consider electrodiagnostic studies to evaluate for concurrent polyneuropathy
- Consider paraneoplastic autoimmune dysautonomia antibody testing (eg, anti- ganglionic acetylcholine receptor, antineuronal nuclear antibody type 1 [ANNA-1], and N-type voltage gated calcium channel antibodies)

## Autonomic Neuropathy

Grading	Management
<b>G1:</b> Mild: No interference with function and symptoms not concerning to patient	<ul style="list-style-type: none"><li>• Low threshold to hold ICI and monitor symptoms for a week. If to continue, monitor very closely for any symptom progression</li></ul>
<b>G2:</b> Moderate: Some interference with ADL, symptoms concerning to patient	<ul style="list-style-type: none"><li>• Hold ICI and resume once return to grade 1</li><li>• Initial observation OR initiate prednisone 0.5-1 mg/kg (if progressing from mild)</li><li>• Neurological consultation</li></ul>
<b>G3-4:</b> Severe: Limiting self-care and aids warranted	<ul style="list-style-type: none"><li>• Permanently discontinue ICI</li><li>• Admit patient</li><li>• Initiate methylprednisolone 1 gram daily x 3 days followed by oral steroid taper</li><li>• Neurologic consultation</li></ul>

## Aseptic Meningitis

**Definition:** May present with headache, photophobia, neck stiffness, often afebrile but may be febrile. There may be nausea/vomiting. Mental status should be normal (distinguishes from encephalitis)

### Diagnostic Work-up:

- MRI of brain with and without contrast + pituitary protocol
- AM cortisol, ACTH to rule out adrenal insufficiency
- Consider lumbar puncture: measure opening pressure; check cell count and protein glucose; and perform Gram stain, culture, PCR for HSV and other viral PCRs depending on suspicion, cytology
- May see elevated WBC with normal glucose, normal culture and Gram stain. May see reactive lymphocytes or histiocytes on cytology

## Aseptic Meningitis

Grading	Management
<p><b>G1:</b> Mild: No interference with function and symptoms not concerning to patient. Note: Any cranial nerve problem should be managed as moderate</p> <p><b>G2:</b> Moderate: Some interference with ADL, symptoms concerning to patient (ie, pain but no weakness or gait limitation)</p> <p><b>G3-4:</b> Severe: Limiting self-care and aids warranted</p>	<ul style="list-style-type: none"><li>• Hold ICI and discuss resumption with patient only after taking into account the risks and benefits</li><li>• Consider empiric antiviral (IV acyclovir) and antibacterial therapy until CSF results</li><li>• Once bacterial and viral infection negative, may closely monitor off corticosteroids or consider oral prednisone 0.5-1 mg/kg or IV methylprednisolone 1 mg/kg if moderate/severe symptoms</li></ul>

## Encephalitis

**Definition:** As for aseptic meningitis, need to exclude infectious causes, especially viral (ie, HSV).

Confusion, altered behavior, headaches, seizures, short-term memory loss, depressed level of consciousness, focal weakness, speech abnormality

### Diagnostic Work-up:

- Neurologic consultation
- MRI of brain with and without contrast may reveal T2/fluid-attenuated inversion recovery changes typical of what is seen in autoimmune encephalopathies or limbic encephalitis or may be normal
- Lumbar puncture: check cell count and protein glucose, and perform Gram stain, culture, PCR for HSV and other viral PCRs depending on suspicion, cytology, oligoclonal bands, autoimmune encephalopathy and paraneoplastic panels
- May see elevated WBC with lymphocytic predominance and/or elevated protein
- EEG to evaluate for subclinical seizures
- Labs: CMP, CBC, ESR, CRP, ANCA (if suspect vasculitic process), thyroid panel including TPO and thyroglobulin
- Rule out concurrent anemia/thrombocytopenia, which can present w severe headaches and confusion

## Encephalitis

Grading	Management
<p><b>G1:</b> Mild: No interference with function and symptoms not concerning to patient. Note: Any cranial nerve problem should be managed as moderate</p> <p><b>G2:</b> Moderate: Some interference with ADL, symptoms concerning to patient (ie, pain but no weakness or gait limitation)</p> <p><b>G3-4:</b> Severe: Limiting self-care and aids warranted</p>	<ul style="list-style-type: none"><li>• Hold ICI and discuss resumption with patient only after taking into account the risks and benefits</li><li>• As above for aseptic meningitis suggest concurrent IV acyclovir until PCR results obtained and negative</li><li>• Trial of methylprednisolone 1-2 mg/kg</li><li>• If severe or progressing symptoms or oligoclonal bands present, consider pulse corticosteroids methylprednisolone 1 gram IV daily for 3-5 days plus IVIG 2 g/kg over 5 days</li><li>• If positive for autoimmune encephalopathy antibody and limited or no improvement, consider rituximab or plasmapheresis in consultation with neurology</li></ul>

## Transverse Myelitis

**Definition:** Acute or subacute weakness or sensory changes bilateral, often with increased deep tendon reflexes

### Diagnostic Work-up:

- Neurologic consultation
- MRI of spine (with thin axial cuts through the region of suspected abnormality) and MRI of brain
- Lumbar puncture: cell count, protein, glucose, oligoclonal bands, viral PCRs, cytology, onconeural antibodies
- Labs: B12, HIV, RPR, ANA, Ro/La, TSH, aquaporin-4 IgG
- Evaluation for urinary retention, constipation

## Transverse Myelitis

Grading	Management
<p><b>G1:</b> Mild: No interference with function and symptoms not concerning to patient. Note: Any cranial nerve problem should be managed as moderate</p> <p><b>G2:</b> Moderate: Some interference with ADL, symptoms concerning to patient (ie, pain but no weakness or gait limitation)</p> <p><b>G3-4:</b> Severe: Limiting self-care and aids warranted</p>	<ul style="list-style-type: none"><li>• Permanently discontinue ICI</li><li>• Methylprednisolone 2 mg/kg</li><li>• Strongly consider higher doses of 1 g/day for 3-5 days</li><li>• Strongly consider IVIG</li></ul>



# HEMATOLOGIC TOXICITIES

## Autoimmune Hemolytic Anemia

**Definition:** A condition in which red blood cells are destroyed and removed from the blood stream before their normal lifespan is over. Symptoms include weakness, paleness, jaundice, dark-colored urine, fever, inability to do physical activity, and heart murmur

### Diagnostic Work-up:

- History and physical examination (with special consideration of history of new drugs, insect, spider or snake bites)
- Blood chemistry, CBC with evidence of anemia, macrocytosis, evidence of hemolysis on peripheral smear; LDH, haptoglobin, bilirubin, reticulocyte count, free hemoglobin
- DIC panel which could include PT/INR infectious causes
- Autoimmune serology
- Paroxysmal nocturnal hemoglobinuria screening
- Direct and indirect bilirubin; LDH; direct agglutinin test; and if no obvious cause, bone marrow analysis, cytogenetic analysis to evaluate myelodysplastic syndromes
- Evaluation for viral/bacterial (mycoplasma etc. ) causes of hemolysis studies
- Protein electrophoresis, cryoglobulin analysis
- Work-up for bone marrow failure syndrome if refractory including B12, folate, copper, parvovirus, iron, thyroid, infection
- Glucose-6-phosphate dehydrogenase
- Evaluation of common drug causes (ribavirin, rifampin, dapsone, interferon, cephalosporins, penicillins, NSAIDs, quinine/quinidine, fludarabine, ciprofloxacin, lorazepam, diclofenac, etc.)
- Assessment of methemoglobinemia

## Autoimmune Hemolytic Anemia

Grading	Management
<b>G1:</b> Hgb < LLN to 10 g/dL	<ul style="list-style-type: none"> <li>Continue ICI with close clinical follow-up and laboratory evaluation</li> </ul>
<b>G2:</b> Hgb < 10-8 g/dL	<ul style="list-style-type: none"> <li>Hold ICI and strongly consider permanent discontinuation</li> <li>Administer 0.5 to 1 mg/kg/day prednisone equivalents</li> </ul>
<b>G3:</b> Hgb < 8 g/dL; transfusion indicated	<ul style="list-style-type: none"> <li>Permanently discontinue ICI</li> <li>Should use clinical judgement and consider admitting the patient</li> <li>Hematology consult</li> <li>Prednisone 1-2 mg/kg/day (oral or IV depending on symptoms/speed of development)</li> <li>If worsening or no improvement, 1 to 2 mg/kg/day prednisone equivalents and permanently discontinue ICI treatment</li> <li>Consider RBC transfusion per existing guidelines. Do not transfuse more than the minimum number of red blood cell (RBC) units necessary to relieve symptoms of anemia or to return a patient to a safe Hgb range (7 to 8 g/dL in stable, noncardiac inpatients)</li> <li>Should offer patients supplementation with folic acid 1 mg once daily</li> </ul>
<b>G4:</b> Life-threatening consequences; urgent intervention indicated	<ul style="list-style-type: none"> <li>Permanently discontinue ICI</li> <li>Admit patient</li> <li>Hematology consult</li> <li>IV prednisone corticosteroids 1-2 mg/kg/day</li> <li>If no improvement or if worsening on corticosteroids or severe symptoms on presentation, initiate other immunosuppressive drugs, such as rituximab, IVIG, cyclosporin A, and mycophenolate mofetil</li> <li>RBC transfusion per existing guidelines. Discuss with blood bank team prior to transfusions that a patient with possible ICI serious adverse event is in house</li> </ul>

### Additional Considerations:

Monitor hemoglobin levels on a weekly basis until the steroid tapering process is complete. Thereafter, less frequent testing is needed

## Acquired Thrombotic Thrombocytopenic Purpura (TTP)

**Definition:** A disorder characterized by the presence of microangiopathic hemolytic anemia, thrombocytopenic purpura, fever, renal abnormalities, and neurological abnormalities, such as seizures, hemiplegia, and visual disturbances. It is an acute or subacute condition

### Diagnostic Workup:

- History with specific questions related to drug exposure (eg, chemotherapy, sirolimus, tacrolimus, antibiotics, quinine)
- Physical exam, peripheral smear
- ADAMTS13 activity level and inhibitor titer
- LDH, haptoglobin, reticulocyte count, bilirubin, urinalysis to rule out other causes
- PT, aPTT, fibrinogen
- Blood group and antibody screen, direct antiglobulin test, CMV serology
- Consider CT/MRI of brain, echocardiogram, electrocardiogram
- Viral studies
- Note: this disorder is usually associated with a severe drop in platelets and hemolysis/anemia precipitously

## Acquired Thrombotic Thrombocytopenic Purpura (TTP)

Grading	Management
<p><b>All Grades</b></p> <p><b>G1:</b> Evidence of RBC destruction (schistocytosis) without anemia, renal insufficiency, or thrombocytopenia clinically</p> <p><b>G2:</b> Evidence of RBC destruction (schistocytosis) without clinical consequence with grade 2 anemia and thrombocytopenia</p>	<ul style="list-style-type: none"> <li>• The first step in the management of TTP is a high index of suspicion for the diagnosis and timely recognition. Hematology consult should immediately be called, as delay in identification is associated with increased mortality/morbidity.</li> <li>• Initially, the patient should be stabilized and any critical organ dysfunction stabilized.</li> </ul>
<p><b>G3:</b> Laboratory findings with clinical consequences (grade 3 thrombocytopenia, anemia, renal insufficiency &gt;2)</p> <p><b>G4:</b> Life-threatening consequences, (eg, CNS hemorrhage or thrombosis/embolism or renal failure)</p>	<ul style="list-style-type: none"> <li>• Hold ICI and discuss resumption with patient only after taking into account the risks and benefits, noting that there is currently no data to recommend restarting ICI therapy</li> <li>• Hematology consult</li> <li>• Administer 0.5 to 1 mg/kg/day prednisone</li> </ul>

## Hemolytic Uremic Syndrome

**Definition:** A disorder characterized by a form of thrombotic microangiopathy with renal failure, hemolytic anemia, and severe thrombocytopenia

Signs and symptoms of HUS can include:

- Bloody diarrhea
- Decreased urination or blood in the urine
- Abdominal pain, vomiting, and occasionally fever
- Pallor
- Small, unexplained bruises or bleeding from the nose and mouth
- Fatigue and irritability
- Confusion or seizures
- High blood pressure
- Swelling of the face, hands, feet or entire body

### Diagnostic Workup:

- History and Physical Exam (special consideration for new history of high risk drugs, hypertension or cardiac causes)
- CBC with indices
- Blood smear morphology. Note that the presence of schistocytes on smear is critical for diagnosis
- Serum creatinine
- ADAMTS13 (to rule out TTP)
- Homocystiene/methylmalonic acid
- Complement testing C3, C4, CH50 (complement inhibitory antibodies for suspected familial)
- Evaluate reticulocyte count and MCV
- Evaluation of infectious cause, including screening for viral EBV, CMV, HHV6
- Evaluation for nutritional causes of macrocytosis (B12 and folate)
- Pancreatic enzymes
- Evaluation for diarrheal causes, shiga toxin, *Escherichia coli* 0157, etc
- Direct antibody test (Coombs test), haptoglobin, LDH, and other etiologies of anemia
- Evaluation for common drugs causing hemolysis (tacrolimus, cyclosporine, sirolimus, etc.)
- Evaluation for concurrent confusion

## Hemolytic Uremic Syndrome

Grading	Management
<b>G1-2:</b> Evidence of RBC destruction (schistocytosis) without clinical consequences of anemia, thrombocytopenia grade 2	<ul style="list-style-type: none"><li>• Continue ICI with close clinical follow-up and laboratory evaluation</li><li>• Supportive care</li></ul>
<b>G3:</b> Laboratory findings with clinical consequences (eg, renal insufficiency, petechiae) <b>G4:</b> Life-threatening consequences, (eg, CNS thrombosis/embolism or renal failure)	<ul style="list-style-type: none"><li>• Permanently discontinue ICI</li><li>• Begin therapy with eculizumab therapy 900 mg weekly x 4 doses, 1200 mg week 5, then 1200 mg every two weeks.</li><li>• Red blood transfusion according to existing guidelines</li></ul>

## Aplastic Anemia

**Definition:** Condition in which the body stops producing enough new blood cells.

### Diagnostic Workup:

- History and physical examination (close attention to medications, exposure to radiation, toxins, recent viral infections)
- CBC, smear, and reticulocyte count
- Viral studies, including CMV, HHV6, EBV, parvovirus
- Nutritional assessments including B12, folate, iron, copper, ceruloplasmin, vitamin D
- Serum LDH, renal function
- Work-up for infectious causes.
- Identify marrow hypo/aplasia
- Bone marrow biopsy and aspirate analysis
- Peripheral blood analysis including neutrophil count, proportion of GPI-negative cells by flow for PNH
- Flow cytometry to evaluate loss of GPI-anchored proteins
- Type and screen patient for transfusions and notify blood bank that all transfusions need to be irradiated and filtered

## Aplastic Anemia

Grading	Management
<p><b>G1:</b> Nonsevere: &gt;0.5 polymorphonuclear cells (PMNs) × 10<sup>9</sup>/L hypocellular marrow, with marrow cellularity &lt;25%, peripheral platelet count &gt;20,000, reticulocyte count &gt;20,000</p>	<ul style="list-style-type: none"><li>• Hold ICI, provide growth factor support and close clinical follow-up and laboratory evaluation</li><li>• Supportive transfusions as per local guidelines</li></ul>
<p><b>G2:</b> Severe: Hypocellular marrow &lt;25% and two of the following: ANC &lt;500, peripheral platelet &lt;20,000, and reticulocyte &lt;20,000</p>	<ul style="list-style-type: none"><li>• Hold ICI and provide growth factor support and close clinical laboratory evaluations daily</li><li>• Administer ATG + cyclosporine. HLA typing and evaluation for bone marrow transplantation if patient is candidate. All blood products should be irradiated and filtered</li><li>• Supportive care with GCSF may be added in addition</li></ul>
<p><b>G3-4:</b> Very Severe: ANC &lt;200, platelet count &lt;20,000, reticulocyte count &lt;20,000, plus hypocellular marrow &lt;25%</p>	<ul style="list-style-type: none"><li>• Hold ICI and monitor weekly for improvement. If not resolved, discontinue treatment until AE has reverted to grade 1</li><li>• Hematology consult, growth factor support</li><li>• Horse ATG plus cyclosporine</li><li>• If no response, repeat immunosuppression with rabbit ATG plus cyclosporine, cyclophosphamide</li><li>• For refractory patients, consider eltrombopag plus supportive care</li></ul>

## Lymphopenia

**Definition:** An abnormally low level of lymphocytes in peripheral blood (PB); for adults, counts of less than 1,500/mm<sup>3</sup>

### Diagnostic Work-up:

- History and physical exam (special attention for lymphocyte-depleting therapy such as fludarabine, ATG, corticosteroids, cytotoxic chemotherapy, radiation exposure etc. as well as history of autoimmune disease, family history of autoimmune disease)
- Evaluation of nutritional state as cause
- Spleen size
- CBC with differential, peripheral smear and reticulocyte counts
- CXR for evaluation of presence of thymoma
- Bacterial cultures and evaluation for infection (fungal, viral, bacterial specifically CMV/HIV)

## Lymphopenia

Grading	Management
<b>G1-2:</b> 500-1000 PB lymphocyte count	<ul style="list-style-type: none"><li>• Continue ICI</li></ul>
<b>G3:</b> 250-499 PB lymphocyte count	<ul style="list-style-type: none"><li>• Continue ICI, checking CBC weekly for monitoring, initiation of CMV screening</li></ul>
<b>G4:</b> <250 PB lymphocyte count	<ul style="list-style-type: none"><li>• Consider holding ICI</li><li>• Initiate <i>Mycobacterium avium</i> complex prophylaxis and <i>Pneumocystis jirovecii</i> prophylaxis, CMV screening. HIV/hepatitis screening if not already done</li><li>• May consider EBV testing if evidence of lymphadenopathy/hepatitis, fevers, hemolysis consistent with lymphoproliferative disease</li></ul>

## Immune Thrombocytopenia (ITP)

**Definition:** An autoimmune disorder characterized by immunologic destruction of otherwise normal platelets

### Diagnostic Work-up:

- History and physical examination (special attention for lymphocyte-depleting therapy such as fludarabine, ATG, corticosteroids, cytotoxic therapy)
- Family history of autoimmunity or personal history of autoimmune disease
- History of viral illness
- CBC
- Peripheral blood smear, reticulocyte count
- Bone marrow evaluation only if abnormalities in the above testing results and further investigation is necessary for a diagnosis
- Patients with newly diagnosed ITP should undergo testing for HIV, HCV, HBV and *H. pylori*
- Direct antigen test should be checked to rule out concurrent Evan syndrome
- Nutritional evaluation
- Bone marrow evaluation if other cell lines affected and concern for aplastic anemia

## Immune Thrombocytopenia (ITP)

Grading	Management
<b>G1:</b> Platelet count <100/ $\mu$ L	Continue ICI with close clinical follow-up and laboratory evaluation
<b>G2:</b> Platelet count <75/ $\mu$ L	<ul style="list-style-type: none"> <li>• Hold ICI, but monitor for improvement. If not resolved, interrupt treatment until AE has reverted to grade 1</li> <li>• Administer prednisone 1 mg/kg/day (dosage range, 0.5–2 mg/kg/day) orally for 2-4 weeks after which time this medication should be tapered over 4-6 weeks to the lowest effective dose</li> <li>• IVIG may be used in conjunction with corticosteroids if a more rapid increase in platelet count is required.</li> </ul>
<b>G3:</b> Platelet count <50/ $\mu$ L  <b>G4:</b> Platelet count <25/ $\mu$ L	<ul style="list-style-type: none"> <li>• Hold ICI, but monitor for improvement. If not resolved, interrupt treatment until AE has reverted to grade 1</li> <li>• Hematology consult</li> <li>• Prednisone corticosteroids 1-2 mg/kg/day (oral or IV depending on symptoms)</li> <li>• If worsening or no improvement, 1-2 mg/kg/day prednisone equivalents and permanently discontinue treatment</li> <li>• IVIG be used with corticosteroids when a more rapid increase in platelet count is required</li> <li>• If IVIG is used, the dose should initially be 1 g/kg as a one-time dose. This dosage may be repeated if necessary</li> <li>• If previous treatment with corticosteroids and/or, IVIG, has been unsuccessful, subsequent treatment may include rituximab, thrombopoietin receptor agonists, or more potent immunosuppression</li> </ul> <p><i>Recommendations from the American Society of Hematology guidelines on immune thrombocytopenia; consult ASH guidelines for further details.<sup>1</sup></i></p>

<sup>1</sup>Neunert C, Lim W, Crowther M, et al; American Society of Hematology. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood*. 2011;117(16):4190-41207.

## Acquired Hemophilia

**Definition:** Disorder caused by the development of autoantibodies (inhibitors) directed against plasma coagulation factors

### Diagnostic Work-up:

- Full blood count to assess platelet number, fibrinogen, PT, PTT, INR. The typical finding in patients with acquired hemophilia A is a prolonged aPTT with a normal PT
- MRI, CT, and ultrasonography may be indicated to localize, quantify, and serially monitor the location and response of bleeding
- Medication review to assess for alternative causes
- Determination of Bethesda unit level of inhibitor

## Acquired Hemophilia

Grading	Management
<b>G1:</b> Mild: 5-40% of normal factor activity in blood; 0.05-0.4 IU/mL of whole blood	<ul style="list-style-type: none"><li>• Hold ICI and discuss resumption with patient only after taking into account the risks and benefits</li><li>• Administer 0.5 to 1 mg/kg/day prednisone</li><li>• Transfusion support as required</li><li>• Treatment of bleeding disorders with hematology consult</li></ul>
<b>G2:</b> Moderate: 1-5% of normal factor activity in blood; 0.01-0.05 IU/mL of whole blood	<ul style="list-style-type: none"><li>• Hold ICI and discuss resumption with patient only after taking into account the risks and benefits</li><li>• Hematology consult</li><li>• Administration of factor replacement (choice based on Bethesda unit of titer)</li><li>• Administer 1 mg/kg/day prednisone ± rituximab (dose 375 mg/m<sup>2</sup> weekly x 4 weeks) and/or cyclophosphamide (dose, 1-2mg/kg/day). Choice of rituximab vs cyclophosphamide is patient specific and should be done with assistance of hematology consult. Prednisone, rituximab, and cyclophosphamide should be given for at least 5 weeks</li><li>• Factors should be provided to increase level during bleeding episodes, with choice of factor based on presence or absence of inhibitor</li></ul>

**G3-4:** Severe: <1% of normal factor activity in blood; < 0.01 IU/mL of whole blood

- Permanently discontinue ICI
- Admit patient
- Hematology consult
- Administration of factor replacement, choice based on Bethesda unit level of inhibitor.
- Bypassing agents may be used (factor VII, factor VIII inhibitor bypass activity). Caution should be taken in the elderly and those with coronary artery disease
- Prednisone corticosteroids 1-2 mg/kg/day (oral or IV depending on symptoms) ± rituximab (dose 375 mg/m<sup>2</sup> weekly x 4 weeks) and/or cyclophosphamide (dose, 1-2 mg/kg/day)
- Transfusion support as required for bleeding
- If worsening or no improvement, should add cyclosporine or immunosuppression/ immunoadsorption

#### **Additional Considerations:**

Acquired Hemophilia requires specialist clinical and laboratory expertise. Consult and/or transfer to a specialist center is often appropriate. If consultation with or transfer to a hemophilia center is not immediately possible, then investigation and treatment should be initiated while a liaison is being established



# CARDIOVASCULAR TOXICITIES

## **Myocarditis, Pericarditis, Arrhythmias, Impaired Ventricular Function with Heart Failure and Vasculitis**

### **Definition:**

Signs and symptoms may include: chest pain, arrhythmia, palpitations, peripheral edema, progressive or acute dyspnea, pleural effusion, fatigue

### **Diagnostic Work-up:**

At baseline

- Electrocardiogram
- Consider Troponin, especially in patient treated with combination immune therapies

Upon signs/symptoms (consider cardiology consult)

- Electrocardiogram
- Troponin
- BNP
- Echocardiogram
- Chest X-ray

Additional testing to be guided by cardiology and may include

- Stress test
- Cardiac catheterization
- Cardiac MRI

## Myocarditis, Pericarditis, Arrhythmias, Impaired Ventricular Function with Heart Failure and Vasculitis

Grading	Management
<p><b>G1:</b> Abnormal cardiac biomarker testing, including abnormal ECG</p> <p><b>G2:</b> Abnormal screening tests with mild symptoms</p> <p><b>G3:</b> Moderately abnormal testing or symptoms with mild activity</p> <p><b>G4:</b> Moderate to severe decompensation, IV medication or intervention required, life threatening conditions</p>	<p>All grades warrant work-up and intervention given potential for cardiac compromise</p> <p>Please consider the following:</p> <ul style="list-style-type: none"> <li>• Hold ICI and permanently discontinue after G1</li> <li>• High-dose corticosteroids (1-2 mg/kg of prednisone) initiated rapidly (oral or IV depending on symptoms)</li> <li>• Admit patient, cardiology consultation</li> <li>• Management of cardiac symptoms according to ACC/AHA guidelines and with guidance from cardiology</li> <li>• Immediate transfer to a coronary care unit should be considered for patients with elevated troponin or conduction abnormalities</li> </ul> <p>In patients without an immediate response to high-dose corticosteroids, consider early institution of cardiac transplant rejection doses of corticosteroids (methylprednisolone 1 g every day) and the addition of either mycophenolate, infliximab, or anti-thymocyte globulin</p>

**Qualifying Statement:** Treatment recommendations are based on anecdotal evidence and the life-threatening nature of cardiovascular complications. Holding checkpoint inhibitor therapy is recommended for all grades of complications. The appropriateness of rechallenging remains unknown. Note that infliximab has been associated with heart failure and is contraindicated at high doses in patients with moderate-severe heart failure.

## Venous Thromboembolism

**Definition:** A disorder characterized by occlusion of a vessel by a thrombus that has migrated from a distal site via the blood stream

Clinical signs and symptoms are variable and may include pain, swelling, increased skin vein visibility, erythema, and cyanosis accompanied by unexplained fever for DVT and dyspnea, pleuritic pain, cough, wheezing or hemoptysis for PE

### Diagnostic Work-up:

- Evaluation of signs and symptoms of PE or DVT may include:
  - Clinical prediction rule to stratify patients with suspected VTE
  - Venous ultra sound for suspected DVT
  - CTPA for suspected PE
- Can also consider D-dimer for low risk patients based on risk stratification by clinical prediction rule for DVT/PE when CT or Doppler not available or appropriate
- Ventilation/perfusion scan is also an option when CTPA is not appropriate
- Consider other testing, including ECG, chest radiography, BNP and troponin levels, and ABG

## Venous Thromboembolism

Grading	Management
<p><b>G1:</b> Venous thrombosis (eg, superficial thrombosis)</p>	<ul style="list-style-type: none"> <li>• Continue ICI</li> <li>• Warm compress</li> <li>• Clinical surveillance</li> </ul>
<p><b>G2:</b> Venous thrombosis (eg, uncomplicated DVT), medical intervention indicated</p> <p><b>G3:</b> Thrombosis (eg, uncomplicated PE [venous], non-embolic cardiac mural [arterial] thrombus), medical intervention indicated</p>	<ul style="list-style-type: none"> <li>• Continue ICI</li> <li>• Management according to CHEST, ACC and/or AHA guidelines and consider consult from cardiology or other relevant specialties</li> <li>• LMWH is suggested over VKA, dabigatran, rivaroxaban, apixaban, or edoxaban for initial and long-term treatment</li> <li>• IV heparin is an acceptable alternative for initial use, and oral anticoagulants are acceptable for the long term</li> </ul>
<p><b>G4:</b> Life-threatening (eg, PE, cerebrovascular event, arterial insufficiency), hemodynamic or neurologic instability, urgent intervention indicated</p>	<ul style="list-style-type: none"> <li>• Permanently discontinue ICI</li> <li>• Admit patient and management according to CHEST, ACC and/or AHA guidelines and with guidance from cardiology</li> <li>• Respiratory and hemodynamic support</li> <li>• LMWH is suggested over VKA, dabigatran, rivaroxaban, apixaban, or edoxaban for initial and long-term treatment</li> <li>• IV heparin is an acceptable alternative for initial use and oral anticoagulants are acceptable for the long term</li> <li>• Further clinical management as indicated based on symptoms</li> </ul>

### Additional Considerations:

- While it may be impossible to determine the etiology of thromboembolic disease in patients with advanced cancer and the role, if any, that ICI treatment plays, it is reasonable to remove the potential inciting agents given the severity and life-threatening potential of grade 4 complications. Clinicians are to use clinical judgement and take into account the risks and benefits when deciding whether to discontinue ICI treatment
- Anticoagulant therapy duration should continue for a minimum of 9-12 months to indefinitely in the setting of active cancer unless patient is asymptomatic, doing well, or in remission



# OCULAR TOXICITIES

Counsel all patients to inform their healthcare provider immediately if they experience any of the following ocular symptoms:

- Blurred vision
- Change in color vision
- Photophobia
- Distortion
- Scotomas
- Visual field changes
- Double vision
- Tenderness
- Pain with eye movement
- Eyelid swelling
- Proptosis

## **Evaluation, Under the Guidance of Ophthalmology:**

- Check vision in each eye separately
- Color vision
- Red reflex
- Pupil size, shape and reactivity
- Fundoscopic examination
- Inspection of anterior part of eye with penlight

## **Prior Conditions:**

- Exclude patients with history of active uveitis
- History of recurrent uveitis requiring systemic immunosuppression or continuous local therapy

## **Additional Considerations:**

- Ocular irAEs are many times seen in the context of other organ irAEs
- High level of clinical suspicion as symptoms may not always be associated with severity
- Best to treat after ophthalmologist eye examination

## Uveitis/Iritis

**Definition:** Inflammation of the middle layer of the eye

**Diagnostic Work-up:** As per page 69

## Uveitis/Iritis

Grading	Management
<b>G1:</b> Asymptomatic	<ul style="list-style-type: none"><li>• Continue ICI</li><li>• Refer to ophthalmology within 1 week</li><li>• Artificial tears</li></ul>
<b>G2:</b> Medical intervention required, anterior uveitis	<ul style="list-style-type: none"><li>• Hold ICI temporarily until after ophthalmology consult</li><li>• Urgent ophthalmology referral</li><li>• Topical corticosteroids, cycloplegic agents, systemic corticosteroids</li><li>• May resume ICI treatment once off systemic corticosteroids which are purely indicated for ocular adverse side effect or once corticosteroids for other concurrent systemic irAE are reduced to <math>\leq 10</math> mg. Continued topical/ocular corticosteroids are permitted when resuming therapy to manage and minimize local toxicity</li><li>• Retreat after return to grade 1 or less</li></ul>
<b>G3:</b> Posterior or panuveitis	<ul style="list-style-type: none"><li>• Permanently discontinue ICI</li><li>• Urgent ophthalmology referral</li><li>• Systemic corticosteroids and intravitreal/periocular/topical corticosteroids</li></ul>
<b>G4:</b> 20/200 or worse	<ul style="list-style-type: none"><li>• Permanently discontinue ICI</li><li>• Emergent ophthalmology referral</li><li>• Systemic corticosteroids (IV prednisone 1-2 mg/kg or methylprednisolone 0.8-1.6 mg/kg) and intravitreal/periocular/topical corticosteroids per ophthalmologist opinion</li></ul>

**Additional Considerations:** Consider use of infliximab or other TNF- $\alpha$  blockers in cases that are severe and refractory to standard treatment

## Episcleritis

**Definition:** Inflammatory condition affecting the episcleral tissue between the conjunctiva and the sclera that occurs in the absence of an infection

**Diagnostic Work-up:** As per page 69

## Episcleritis

Grading	Management
<b>G1:</b> Asymptomatic	<ul style="list-style-type: none"><li>• Continue ICI</li><li>• Refer to ophthalmology within 1 week</li><li>• Artificial tears</li></ul>
<b>G2:</b> Vision 20/40 or better	<ul style="list-style-type: none"><li>• Hold ICI therapy temporarily until after ophthalmology consult</li><li>• Urgent ophthalmology referral</li><li>• Topical corticosteroids, cycloplegic agents, systemic corticosteroids</li></ul>
<b>G3:</b> Symptomatic and vision worse than 20/40	<ul style="list-style-type: none"><li>• Permanently discontinue ICI</li><li>• Urgent ophthalmology referral.</li><li>• Systemic corticosteroids and topical corticosteroids with cycloplegic agents</li></ul>
<b>G4:</b> 20/200 or worse	<ul style="list-style-type: none"><li>• Permanently discontinue ICI</li><li>• Emergent ophthalmology referral.</li><li>• Systemic corticosteroids and topical corticosteroids with cycloplegic agents</li></ul>

**Additional Considerations:** Consider use of infliximab or other TNF- $\alpha$  blockers in cases that are severe and refractory to standard treatment

## Blepharitis

**Definition:** Inflammation of the eyelid that affects the eyelashes or tear production

**Diagnostic Work-up:** As per page 69

## Blepharitis

Grading	Management
No formal grading system	<ul style="list-style-type: none"><li>• Warm compresses and lubrication drops</li><li>• Continue therapy unless persistent and serious</li></ul>

## Abbreviations:

**ABG**=arterial blood gas; **ACC**=American College of Cardiology; **ACTH**=adrenocorticotropic hormone; **ADL**=activities of daily living; **AE**=adverse event; **AHA**=acquired hemophilia A; **AHA**=American Heart Association; **AI**=adrenal insufficiency; **ALT**=alanine aminotransferase; **ANA**=antinuclear antibodies; **ANCA**=antineutrophil cytoplasmic antibodies; **ANNA-1**=anti-neuronal nuclear antibody 1; **aPTT**=activated partial thromboplastin time; **ASCO**=American Society of Clinical Oncology; **ASH**=American Society of Hematology; **ASMA**=anti-smooth muscle antibodies; **AST**=aspartate aminotransferase; **ATG**=antithymocyte globulin; **BAL**=bronchoalveolar lavage; **BNP**=brain natriuretic peptide; **BSA**=body surface area; **CAR-T**=chimeric antigen receptor T-cell; **CBC**=complete blood count; **CMP**=comprehensive metabolic panel; **CMV**=cytomegalovirus; **CNS**=central nervous system; **CPK**=creatinine phosphokinase; **CRP**=C-reactive protein; **CSF**=cerebrospinal fluid; **CT**=computed tomography; **CTCAE**=Common Terminology Criteria for Adverse Events; **CTLA-4**=cytotoxic T-cell lymphocyte-4; **CTPA**=computed tomographic pulmonary angiography; **CXR**=chest x-ray; **DAT**=direct antiglobulin test; **DIC**=disseminated intravascular coagulation; **DEB**=diepoxybutane; **DKA**=diabetic ketoacidosis; **DM**=diabetes mellitus; **DVT**=deep vein thrombosis; **EBV**=Epstein-Barr virus; **EEG**=electroencephalogram; **EGD**=esophagogastroduodenoscopy; **EMG**=electromyography; **EMS**=emergency medical services; **ENT**=ears, nose, and throat; **ESR**=erythrocyte sedimentation rate; **FLAIR**=fluid-attenuated inversion recovery; **FSH**=follicle-stimulating hormone; **FT4**=free thyroxine; **G1**=grade 1; **G2**=grade 2; **G3**=grade 3; **G4**=grade 4; **GBS**=Guillain-Barre' syndrome; **GCSF**=granulocyte colony-stimulating factor; **GI**=gastrointestinal; **GPI**=glycosylphosphatidylinositol; **HCV**=hepatitis C virus; **Hgb**=hemoglobin; **HHV6**=human herpesvirus 6; **HIV**=human immunodeficiency virus; **HRCT**=high-resolution computed tomography; **HSV**=herpes simplex virus; **HUS**=hemolytic uremic syndrome; **IA**=inflammatory arthritis; **ICI**=immune checkpoint inhibitor; **ICU**=intensive care unit; **IgG**=immunoglobulin G; **irAE**=immune-related adverse event; **ITP**=idiopathic thrombocytopenic purpura; **IV**=intravenous; **IVIG**=intravenous immunoglobulin; **LEMS**=Lambert-Eaton Myasthenic Syndrome; **LFTs**=liver function tests; **LH**=lutening hormone; **LLN**=lower limit of normal; **LMWH**=low molecular weight heparin; **MCV**=mean corpuscular volume; **MDS**=myelodysplastic syndromes; **MGFA**=myasthenia gravis foundation of America; **MMF**=mycophenolate mofetil; **MRI**=magnetic resonance imaging; **NCS**=nerve conduction study; **NIF**=negative inspiratory force; **O&P**=ova and parasite; **PCP**=Pneumocystis pneumonia; **PCR**=polymerase chain reaction; **PD-1**=programmed death 1; **PD-L1**=programmed death ligand 1; **PE**=pulmonary embolism; **PEX**=plasma exchange; **PMNs**=polymorphonuclear cells; **PNH**=paroxysmal nocturnal hemoglobinuria; **PPI**=proton pump inhibitor; **PT**=prothrombin time; **PTU**=propylthiouracil; **RBC**=red blood cell; **RPR**=rapid plasma reagin; **T1DM**=type 1 diabetes mellitus; **T2DM**=type 2 diabetes mellitus; **TB**=tuberculosis; **TD**=three times a day; **TPO**=thyroid peroxidase; **TSH**=thyroid stimulating hormone; **TSI**=thyroid stimulation immunoglobulin; **TTE**=transthoracic echocardiogram; **TTP**=thrombotic thrombocytopenic purpura; **ULN**=upper limit of normal; **US**=ultrasound; **UTIs**=urinary tract infections; **V/Q**=ventilation-perfusion lung scan; **VC**=vital capacity; **VKA**=vitamin K antagonists; **VTE**=venous thromboembolism; **WBC**=white blood cell



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