ASCO Guidelines

MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS IN PATIENTS TREATED WITH IMMUNE CHECKPOINT INHIBITOR THERAPY: AMERICAN SOCIETY OF CLINICAL ONCOLOGY CLINICAL PRACTICE GUIDELINE		
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1.0 SKIN TOXICITY	
1.1 Rash/Inflammatory Dermatitis **Definition:** Erythema multiforme minor (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 EM major, it and 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 non-pustular, non-bullous measles-like exanthematous rash of the skin often referred to as "maculopapular" and without systemic symptoms or lab abnormalities excluding occasional isolated peripheral eosinophilia, Palmoplantar erythrodysaesthesia (PPE) (hand-foot syndrome) (redness, numbness/burning/itching and superficial desquamation of the palms and soles), neutrophilic dermatoses (e.g. sweet's syndrome) and others.	
Diagnostic Workup: • 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, ds-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	
Grading Grading according to CTCAE criteria is a challenge for skin. Instead, severity may be based on BSA, tolerability, morbidity, and duration.	**Management**
G1: Symptoms do not affect the quality of life or controlled with topical regimen and/or oral antipruritic	• Continue ICPi • Treat with topical emollients and/or mild-moderate potency topical corticosteroids • Counsel patients to avoid skin irritants and sun exposure
G2: Inflammatory reaction that affects quality of life and requires intervention based on diagnosis.	• Consider holding ICPi and monitor weekly for improvement. If not resolved, interrupt treatment until skin AE has reverted to grade 1 • Consider initiating prednisone (or equivalent) at dosing 1 mg/kg tapering over at 4 weeks • In addition, treat with topical emollients, oral antihistamines and medium-to-high potency topical corticosteroids
G3: As grade 2 but with failure to respond to indicated interventions for a grade 2 dermatitis.	• Hold ICPi therapy and consult with dermatology to determine appropriateness of resuming • Treat with topical emollients, oral antihistamines and high potency topical corticosteroids • Initiate oral prednisone or equivalent (0.5-1 mg/kg/day) tapering over at least 4 weeks
G4: All severe rashes	• Immediate hold ICPi and consult dermatology to determine appropriateness of resuming ICPi therapy upon

unmanageable with prior interventions and intolerable.	resolution of skin toxicity and once corticosteroids are reduced to prednisone (or equivalent) 10mg or less. • Systemic steroids: IV methylprednisolone (or equivalent) dosed at 1–2mg/kg with slow tapering when the toxicity resolves • Monitor closely for progression to Severe Cutaneous Adverse Reaction • Should admit patient immediately with direct oncology involvement and with an urgent consult by dermatology • Consider alternative antineoplastic therapy over resuming ICPi's if the skin irAE does not resolve to grade 1 or less. If ICPI's are the patient's only option, consider restarting once these side effects have resolved to a grade 1 level.
1.2 Bullous Dermatoses **Definition:** including bullous pemphigoid or other autoimmune bullous dermatoses , bullous drug reaction	
Diagnostic Workup: • 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 (e.g. herpes simplex, herpes zoster, bullous impetigo, bullous insect bite, friction or pressure blister, etc.) • Consider skin biopsy (both H+E evaluation of lesional skin and direct immunofluorescence evaluation of peri-lesional skin),	
Grading	**Management**
G1: Asymptomatic, Blisters Covering < 10% BSA and no associated erythema	• If blisters are <10% BSA, are asymptomatic and non-inflammatory (such as the case with friction blisters or pressure blisters), cessation of ICPi is not necessary and only observation/local wound care is warranted. • 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 • See grade 2 management recommendations.
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 ICPi 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 • Workup 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: o 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. o 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 drug-induced hypersensitivity syndrome/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 apply friction parallel to the skin surface. Nikolsky sign is positive if this results in detached or sloughing epidermis demonstrating poor attachement of the epidermis to the dermis, which is the case in some autoimmune disorders (e.g. pemphigus) and SJS/TEN
G3: Skin sloughing covering >30% BSA with associated pain and limiting self care ADL	• Hold ICPi therapy and consult with dermatology to determine appropriateness of resuming • Administer IV methylprednisolone (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 steroids 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 ICPi • Admit patient immediately and place under supervision of a dermatologist • Administer IV methylprednisolone (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 longterm use of systemic steroids 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.
1.3 Severe Cutaneous Adverse Reactions (SCAR), 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 Workup: • 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 pusulosis (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 drug-induced hypersensitivity syndrome/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 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 (e.g. pemphigus) and SJS/TEN.

Grading	Management
All Grades	In cases of suspected SJS or any mucous membranes involvement, discontinue ICPi treatment and monitor closely for improvement regardless of grade.
G1: N/A	For the SCAR adverse reactions, 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 progess to grade 3 or 4.
G2: Morbilliform ("maculopapular") exanthem covering 10-30% BSA with systemic symptoms, lymphadenopathy or facial swelling	• Hold ICPi and monitor patients closely every 3 days with grade 2 irAE's for progression to involvement of greater body surface area and/or mucous membrane involvement. • Consider following patients closely using serial photography. • Initiate therapy with topical emollients, oral antihistamines and medium-to-high strength topical corticosteroids • Consider initiation of prednisone (or equivalent) 0.5-1 mg/kg tapered over at least 4 weeks
G3: Skin sloughing covering <10% BSA with mucosal involvement associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment)	• Hold ICPi therapy and consult with dermatology • 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 • Administer IV methylprednisolone (or equivalent) 0.5 -1 mg/kg and convert to oral corticosteroids on response, wean over at least 4 weeks • 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. • Given the immune mechanism of action of these medicines, use of immune suppression is warranted and should be offered.

	• For mucous membrane involvement of SJS or toxic epidermal necrolysis (TEN), appropriate consulting services should be offered to guide management in preventing sequelae from scarring (e.g. ophthalmology, eyes nose and throat, urology, gynecology, etc. as appropriate)
G4: Skin erythema and blistering/sloughing covering ≥10 to > 30% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment) and/or systemic symptoms and concerning associated blood work abnormalities (e.g. LFT elevations in the setting of DRESS/DIHS)	• Permanently discontinue ICPi • 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 (e.g. optholmology, urology, gynechology, Ear, Nose and Throat Surgery, etc.) • Initiate IV methylprednisolone (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/Drug Hypersensitivity Syndrome.	
2.0 GASTOINTESTINAL TOXICITY	
2.1 Colitis **Definition:** A disorder characterized by inflammation of the colon.	
Diagnostic Workup: G2: • Work up of blood (CBC, CMP, TSH, ESR, CRP), stool (culture, C. diff, parasite, CMV or other viral etiology, O&P, 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 e.g. 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 ICPi.	
Grading (Based on CTCAE for diarrhea, as most often used clinically)	**Management**
All Patients	Counsel all patients to be aware of and inform their healthcare provider immediately if they experience:

	• abdominal pain, nausea, cramping, blood or mucus in stool or changes in bowel habits • fever, abdominal distention, obstipation, constipation For Grade ≥2, consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to Grade ≤1; concurrent immunosuppressant maintenance therapy should be considered only if clinically indicated in individual cases
G1: Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	• Continue ICPi. Alternatively, ICPi may be held temporarily and resumed if toxicity does not exceed grade 1 • Monitor for dehydration and recommend dietary changes • Facilitate expedited phone contact with patient/caregiver • May obtain gastroenterology consult for prolonged G1 cases
G2: Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	• Should hold ICPi temporarily until patient's symptoms recover to G1. Can consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to Grade ≤1. • 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 Imodium if infection has been ruled out • Should consult with gastroenterology for G≥2 • 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 the risks and benefits • EGD/colonoscopy, endoscopy evaluation should be highly recommended for cases grade ≥ 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 grade ≥ 2 to differentiate functional vs inflammatory diarrhea, and use calprotectin to monitor treatment response if provider prefers • Repeat colonoscopy is optional for cases grade ≥ 2 for disease activity monitoring to achieve complete remission, especially if there is a plan to resume ICPi
G3: Increase of ≥7 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. • 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 ≥3 to 5 days or recur after improvement consider administering intravenous steroid or non-corticosteroid (e.g., 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 (i.e., CMV colitis) and for anti-TNF or steroid refractory
G4: Life-threatening consequences;	• Permanently discontinue treatment

urgent intervention indicated	• Should admit patient when clinically indicated. Patients managed as outpatients should be very closely monitored • Administer 1 to 2 mg/kg/day methylprednisolone or equivalent until symptoms improve to grade 1, and then start taper over 4-6 weeks. • Consider early infliximab 5-10mg/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-a blocker. The decision should be made on an individual basis from gastroenterology and oncology evaluation. This is based on case series showing promising results.[1,2] • Patients with hepatitis and irAE colitis are rare and management should include permanently discontinuing ICPi 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 as colitis including steroid and/or infliximab etc.	
2.2 Hepatitis **Definition:** A disorder characterized by a viral pathologic process involving the liver parenchyma	
Diagnostic Workup: • 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: • 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 ANA/ASMA/ANCA. If patients with elevated ALKP alone, GGT should be tested. For isolated elevation of transaminases, consider checking Creatine Kinase for other etiologies.	
Grading	**Management**
All Patients	Counsel all patients to be aware of and inform their healthcare provider immediately if they experience • Yellowing of skin or whites of the eyes • Severe nausea or vomiting • Pain on the right side of the abdomen • Drowsiness • Dark urine (tea colored) • Bleeding or bruising more easily than normal • Feeling less hungry than usual
G1: Asymptomatic (AST or ALT >ULN to 3.0x ULN and/or total bilirubin >ULN to 1.5x ULN)	• Continue ICPi with close monitoring; consider alternate etiologies • Monitor labs 1 to 2 times weekly • Manage with supportive care for symptom control
G2: Asymptomatic (AST or ALT >3.0 to ≤5x ULN and/or total bilirubin >1.5 to ≤3x ULN)	• Hold ICPi temporarily and resume if recover to ≤ Grade 1 on prednisone ≤ 10mg/day • 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

	• Increase frequency of monitoring to every 3 days • 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 showing the liver toxicity from infliximab from other studies) • In follow-up, may resume ICPi treatment follow by taper only when symptoms improve to grade 1 or less and steroid ≤ 10mg/day. Taper over at least 1 month. • Patients should be advised to stop unnecessary medications and any known hepatotoxic drugs
G3: Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis; reactivation of chronic hepatitis (AST or ALT 5-20x ULN and/or total bilirubin 3-10 ULN)	• Permanently discontinue ICPi • Immediately start steroid 1-2 mg/kg methylprednisolone or equivalents • If steroid refractory or no improvement after 3 days, consider mycophenolate mofetil or azathioprine (if using Azathioprine should test for thiopurine methyltransferase (TPMT) deficiency) • Labs at daily/qod; consider inpatient monitoring for patients with AST/ALT > 8 ULN and/or elevated TB 3 ULN • Increase frequency of monitoring to every 1 to 2 days • 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 the liver toxicity from infliximab from other studies). Alternatives include non TNFα agents as systemic immunosuppressants • If no improvement is achieved with steroid 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 • Steroid taper can be attempted around 4-6 weeks, re-escalate if needed, optimal duration unclear
G4: Decompensated liver function (e.g., ascites, coagulopathy, encephalopathy, coma) (AST or ALT >20x ULN and/or total bilirubin >10x ULN)	• Permanently discontinue ICPi • 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 ≤G1, re-escalate if needed, optimal duration unclear • Consider transfer to tertiary care facility if necessary
3.0 LUNG TOXICITY	
3.1 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 Workup • Should include the following: CXR, CT, pulse oximetry; • For G2 or higher, may include the following infectious workup: nasal swab, sputum culture and sensitivity, blood culture and sensitivity, urine culture and sensitivity	
Grading	**Management**

G1: Asymptomatic; confined to one lobe of the lung or less than 25% of lung parenchyma; clinical or diagnostic observations only	• Hold ICPi with radiographic evidence of pneumonitis progression • 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 • May resume ICPi with radiographic evidence of improvement or resolution. If no improvement, should treat as G2 • Monitor patients weekly with history and physical examination, pulse oximetry; may also offer CXR
G2: Symptomatic; Involves more than one lobe of the lung or 25-50% of lung parenchyma; medical intervention indicated; limiting instrumental ADL	• Hold ICPi until resolution to grades ≤1 • Prednisone 1-2 mg/kg/day and taper by 5-10 mg/week over 4-6 weeks • Consider bronchoscopy with BAL • Consider empiric antibiotics • Monitor Q3 days with history and physical examination, pulse oximetry, consider CXR; No clinical improvement after 48-72 hours of prednisone, treat as grade 3.
G3: Severe symptoms; Hospitalization required: Involves all lung lobes or > 50% of lung parenchyma; limiting self care ADL; oxygen indicated.	• Permanently discontinue ICPi • Empiric antibiotics; methylprednisolone IV 1-2 mg/kg/day; No improvement after 48 hours, may add infliximab 5 mg/kg or mycophenolate mofetil IV 1 g BID or IVIG X 5 days or cyclophosphamide. Taper corticosteroids over 4-6 weeks
G4: Life-threatening respiratory compromise; urgent intervention indicated (intubation)	• 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 Bactrim may be offered to patients on prolonged steroid use (>12 weeks), according to institutional guidelines[3-6] • 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[7] • Bronchoscopy + Biopsy – if clinical picture is consistent with pneumonitis, no need for biopsy	
4.0 ENDOCRINE TOXICITY	
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	
4.1 THYROID	
4.1.1 Primary Hypothyroidism **Definition:** Elevated TSH, normal or low FT4	
Diagnostic Workup: • TSH and FT4 every 4-6 weeks as part of routine clinical monitoring on therapy or for case detection in symptomatic patients	
Grading	**Management**
G1: TSH <10 mIU/L and asymptomatic	• Should continue ICPi with close follow-up and monitoring of TSH, fT4
G2: Moderate symptoms, Able to Perform ADL. TSH persistently >10 mIU/L	• May hold ICPi until symptoms resolve to baseline • Consider endocrine consultation • Prescribe thyroid hormone supplementation in symptomatic patients with any degree of TSH elevation or in asymptomatic patients with TSH levels that persist over 10 mIU/L (measured 4 weeks apart). • Monitor TSH every 6-8 weeks while titrating hormone replacement to normal TSH. • 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. • Once adequately treated, should monitor thyroid function (at least TSH) every 6 weeks while on active ICPi therapy or as needed for symptoms to ensure appropriate replacement. Repeat testing annually or as indicated by symptoms once stable
G3-4: Severe symptoms, medically significant or life-threatening consequences, Unable to Perform ADL	• Hold ICPi until symptoms resolve to baseline with appropriate supplementation • Endocrine consultation • May admit for IV therapy if signs of myxedema (bradycardia, hypothermia). • Thyroid supplementation and reassessment as in G2
Additional Considerations • For patients without risk factors, full replacement can be estimated with an ideal body weight based dose of approximately 1.6mcg/kg/day. • For elderly or fragile patients with multiple comorbidities, consider titrating up from low dose, starting at 25-50mcg. • 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.	
4.1.2 Hyperthyroidism **Definition:** Suppressed TSH and high normal or elevated FT4 and/or T3.	

Diagnostic Workup: • 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 (e.g. ophthalmopathy). • Close monitoring of thyroid function every 2-3 weeks after diagnosis to catch transition to hypothyroidism in patients with thyroiditis and hyperthyroidism.	
Grading	**Management**
G1: Asymptomatic or mild symptoms	• Can continue ICPi 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 4.1.1).
G2: Moderate symptoms, Able to Perform ADL	• Consider holding ICPi until symptoms return to baseline • Consider endocrine consultation • Beta-blocker (e.g. atenolol or propranolol) for symptomatic relief. • Hydration and supportive care • Corticosteroids are not usually required to shorten duration. • For persistent hyperthyroidism (>6 weeks) or clinical suspicion, work up for Graves' disease (TSI or TRAb) and consider thionamide (methimazole or PTU). • Refer to Endocrinology for Graves disease.
G3-4: Severe symptoms, medically significant or life-threatening consequences, Unable to Perform ADL	• Hold ICPi until symptoms resolve to baseline with appropriate therapy • Endocrine consultation • Beta-blocker (e.g. atenolol or propranolol) for symptomatic relief. • For severe symptoms or concern for thyroid storm, hospitalize patient and initiate prednisone 1-2mg/kg/day or equivalent tapered over 1-2 weeks. Consider also use of SSKI or thionamide (methimazole or PTU).
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.	
4.2 ADRENAL - Primary adrenal insufficiency (AI) **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 Workup for patients in whom adrenal insufficiency is suspected:
• Evaluate ACTH (AM), cortisol level (AM)
• Basic Metabolic Panel (Na, K, CO2, 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	

Grading	**Management**
G1: Asymptomatic or mild symptoms	• Consider holding ICPi until patient is stabilized on replacement hormone.

	• Endocrine consultation • Replacement therapy with prednisone (5-10mg daily) or hydrocortisone (10-20mg po qAM, 5-10mg po q2PM) • May require fludrocortisone (0.1mg/day) for mineralocorticoid replacement in primary adrenal insufficiency. • Titrate dose up or down as symptoms dictate
G2: Moderate symptoms, Able to Perform ADL	• Consider holding ICPi until patient is stabilized on replacement hormone. • Endocrine consultation • Initiate outpatient treatment at 2-3 times maintenance (e.g. if prednisone, 20 mg daily; if hydrocortisone 20-30 mg on the morning and 10-20 mg in the afternoon) to manage acute symptoms. • Taper stress dose corticosteroids down to maintenance doses over 5-10 days. • Maintenance therapy as in G1.
G3-4: Severe symptoms, medically significant or life-threatening consequences, Unable to Perform ADL	• Hold ICPi until patient is stabilized on replacement hormone. • Endocrine consultation • See in clinic or, after hours, make an ER referral for: o Normal saline (at least 2L) o IV Stress dose steroids 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 G1
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 4.3 • Patients on corticosteroids for management of other conditions, will have low morning cortisol as a result of iatrogenic, secondary AI. ACTH will also be low in these patients. A diagnosis of AI is challenging to make in these situations (see below section on hypophysitis). • Emergent therapy for someone with *suspected* AI 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.	
4.3 PITUITARY - 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 Workup: Diagnosis: Low ACTH with a low cortisol. Low or normal TSH with a low FT4. Hypernatremia and volume depletion with DI. Low testosterone or estradiol with low LH and FSH. Testing: • Evaluate ACTH, cortisol (AM), TSH, free T4, 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 brain w/wo contrast with pituitary/sellar cuts in patients with multiple endocrine abnormalities +/- new severe headaches or complaints of vision changes	
Grading	**Management**
G1: Asymptomatic or mild symptoms	• Considering holding ICPi until patient is stabilized on replacement hormones. • Hormonal supplementation as needed, using dosing as above for primary hypothyroidism and adrenal insufficiency (e.g. hydrocortisone 10-20 mg orally in the morning, 5-10 mg orally in early afternoon; levothyroxine by weight). • Testosterone or estrogen therapy as needed in those without contraindications. • Endocrine consultation • Always start corticosteroids several days before thyroid hormone to prevent precipitating adrenal crisis • Follow FT4 for thyroid hormone replacement titration (TSH is not accurate).
G2: Moderate symptoms, Able to Perform ADL	• Consider holding ICPi until patient is stabilized on replacement hormones. • Endocrine consultation • Hormonal supplementation as in G1
G3-4: Severe symptoms, medically significant or life-threatening consequences, Unable to Perform ADL	• Hold ICPi until patient is stabilized on replacement hormones. • Endocrine consultation • Hormonal supplementation as in G1 • Consider initial pulse dose therapy with Prednisone 1-2mg/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. • Workup cannot be done with a simple AM cortisol in a patient on corticosteroids for other conditions. • Laboratory confirmation of AI 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	
4.4 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 Workup: • 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 X 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-GAD, anti-Islet Cell or anti-Insulin antibodies are highly specific for autoimmune diabetes. Insulin and c-peptide levels can also assist in the diagnosis.	
Grading	**Management**

G1: Asymptomatic or mild symptoms; Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/LNo evidence of ketosis or laboratory evidence of T1DM	• Can continue ICPi with close clinical follow-up and laboratory evaluation • May initiate oral therapy for those with new onset T2DM. • Screen for T1DM if appropriate for example acute onset with prior normal values or clinical concern for ketosis
G2: Moderate symptoms, Able to Perform Activities of Daily Living; Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L. Ketosis or evidence of T1DM at any glucose level	• May hold ICPi until glucose control is obtained. • Titrate oral therapy or add insulin for worsening control in T2DM. • Should administer insulin for T1DM (or as default therapy if there is confusion about type) • Urgent Endocrine consultation for any patient with T1DM. In the absence of endocrinology, internal medicine may suffice • Consider admission for T1DM if early outpatient evaluation is not available or signs of ketoacidosis are present.
G3-4: Severe symptoms, medically significant or life-threatening consequences, Unable to Perform Activities of Daily Living; G3: >250 - 500 mg/dL; >13.9 - 27.8 mmol/L; G4: >500 mg/dL; >27.8 mmol/L	• Hold ICPi until glucose control is obtained on therapy with reduction of toxicity to grade 1 or less. • Urgent Endocrine consultation for all patients. • Initiate insulin therapy for all patients. • Admit for inpatient management : o Concerns for developing DKA o Symptomatic patients regardless of diabetes type o New onset T1DM unable to see Endocrinology.
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.	
5.0 MUSCULOSKELETAL TOXICITY	
5.1 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 mins-1 hour. Improvement of symptoms with NSAIDs or corticosteroids, but not with opioids or other pain meds may also be suggestive of IA	
Diagnostic Workup: 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 imaging of affected joints if clinically indicated (e.g. 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

Grading	Management
All Grades	Clinicians should follow reports of new joint pain to determine if IA is present. Question whether symptom new since receiving ICPi.
G1: Mild pain with inflammation, erythema, or joint swelling	• Continue ICPi • Initiate analgesia with acetaminophen and/or NSAIDs
G2: Moderate pain associated with signs of inflammation, erythema, or joint swelling; limiting instrumental ADL	• Hold ICPi and resume upon symptom control and on prednisone ≤ 10mg/day • Escalate analgesia and consider higher doses of NSAIDS as needed • If inadequately controlled, initiate prednisone or prednisolone 10-20 mg/day or equivalent x 4-6 weeks • If improvement, slow taper according to response during the next 4-6 weeks. If no improvement after initial 4-6 weeks treat as G3. • If unable to lower corticosteroid dose to below 10mg/d after 3 months, consider disease-modifying antirrheumatic drug (DMARD) • Consider intra-articular steroid injections for large joints • Referral to rheumatology

G3-4: Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self care ADL	• Hold ICPi temporarily and may resume in consultation with rheumatology, if recover to ≤G1
	• Initiate oral prednisone 0.5-1 mg/kg
	• If failure of improvement after 4 weeks or worsening in meantime – consideration of synthetic or biologic disease-modifying antirrheumatic drug (DMARD)
	  • Synthetic: methotrexate, leflunomide;
	  • Biologic: Consider anti-cytokine therapy such as TNFα or IL6 receptor inhibitors. Note: As caution, IL6 inhibition can cause intestinal perforation. While this is extremely rare, it should not be used in patients with colitis
	• Test for viral hepatitis B, C and latent/active TB test prior to DMARD treatment
	• Referral to rheumatology

Additional Considerations:

- Early recognition is critical to avoid erosive joint damage
- Corticosteroids can be used as part of initial therapy in IA, 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 steroids, consider early referral
- Consider PCP prophylaxis for patients treated with high dose of corticosteroids for longer than 12 weeks, as per local guidelines

5.2 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 Workup:
- 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 electromyography (EMG), imaging (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

Grading	Management
G1: Mild weakness with or without pain	• Continue ICPi • If CK is elevated and patient has muscle weakness may offer oral corticosteroids, and treat as grade 2 • Offer analgesia with acetaminophen or NSAIDs if there are no contraindications
G2: Moderate weakness with or without pain limiting age-appropriate instrumental ADL	• Hold ICPi temporarily and may resume upon symptom control, if CK is normal and prednisone dose < 10mg; if worsens, treat as per G3 • NSAIDs as needed • Referral to rheumatologist or neurologist • If CK is elevated (x3 or more), initiate prednisone or equivalent at 0.5-1 mg/kg • May require permanent discontinuation of ICPi in most cases with G2 symptoms and objective findings (elevated enzymes, abnormal EMG, abnormal muscle MRI or biopsy).

G3-4: Severe weakness with or without pain; limiting self care ADL	• Hold ICPi until grade ≤1 off immune suppression and permanently discontinue if any evidence of myocardial involvement • Consider hospitalization for severe weakness • Referral to rheumatologist or neurologist • Initiate prednisone 1 mg/kg or equivalent. Consider 1-2mg/kg of methylprednisolone IV or higher dose bolus if severe compromise (weakness severely limiting mobility, cardiac, respiratory, dysphagia). • Consider plasmapheresis • Consider IVIG therapy • 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
Additional Considerations: • Caution is advised with rechallenging	
5.3 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 Workup: **G1**: Complete rheumatological 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	
Grading	**Management**
G1: Mild stiffness and pain	• Continue ICPi • Initiate analgesia with acetaminophen and/or NSAIDs if there are no contraindications
G2: Moderate stiffness and pain ; limiting age-appropriate instrumental ADL	• Consider holding ICPi and resuming upon symptom control, prednisolone < 10mg; if worsens, treat as per G3 • Initiate prednisone 20 mg/d or equivalent. If symptoms improve, start to taper dose after 3-4 weeks. • If no improvement or need for higher dosages after 4 weeks, escalate to G3 • Consider referral to rheumatology

G3-4: Severe stiffness and pain; limiting self care ADL	• Hold ICPi and may resume, in consultation with rheumatology, if recover to ≤G1. However, note that cases of toxicity returning upon rechallenge have been reported. • Referral to rheumatology • Should initiate prednisone 20 mg/d or equivalent. If no improvement or need for higher dosages for prolonged time, may offer a steroid sparing agent such as methotrexate or IL6 inhibition with tocilizumab. Note: As caution, IL6 inhibition can cause intestinal perforation. While this is extremely rare, it should not be used in patients with colitis or GI metastases • Consider admission for pain control
6.0 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	
6.1 Nephritis **Definition:** Inflammation of the kidney affecting the structure	
Grading	**Management**
G1: Creatinine level increase of >0.3 mg/dL; creatinine 1.5 - 2.0x above baseline	• Consider temporarily holding ICPi, pending consideration of potential alternative etiologies (recent IV contrast, medications, fluid status) and baseline renal function. A change that is still <1.5 ULN *could* be meaningful
G2: Creatinine 2 - 3x above baseline	• Hold ICPi temporarily • Consult nephrology • 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 • If worsening or no improvement: 1 to 2 mg/kg/day prednisone equivalents and permanently discontinue treatment • If improved to G1 or less taper steroids over 4-6 weeks. • If no recurrence of CRI discuss resumption of ICPI with patient after taking into account the risks and benefits.
G3: Creatinine >3 x baseline or >4.0 mg/dL; hospitalization indicated	• Permanently discontinue ICPi • Consult nephrology • Evaluate for other causes (recent IV contrast, medications, fluid status etc.) • Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent)
G4: Life-threatening consequences; dialysis indicated	
Additional Considerations: Monitor creatinine weekly. Reflex kidney biopsy should be discouraged until steroid treatment has been attempted.	
6.2 Symptomatic Nephritis – Follow Up	
Grading	**Management**

G1	If improved to baseline • Resume routine creatinine monitoring
G2	If improved to Grade 1: • Taper corticosteroids over at least 3 weeks before resuming treatment with routine creatinine monitoring If elevations persist > 7 days or worsen and no other cause found, treat as Grade 3
G3	If improved to Grade 1: • Taper corticosteroids over at least 4 weeks If elevations persist > 3-5 days or worsen, consider additional immunosuppression (e.g. mycophenolate)
G4	If improved to Grade 1: • Taper corticosteroids over at least 4 weeks If elevations persist > 2-3 days or worsen, consider additional immunosuppression (e.g. mycophenolate).
7.0 NERVOUS SYSTEM TOXICITY	
7.1 Myasthenia Gravis **Definition: Fatigable** or fluctuating muscle weakness, generally proximal>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 ICPi may have overlapping symptoms.	
Diagnostic Workup: • 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 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, EKG and TTE for possible concomitant myocarditis • Neurological consultation • Electrodiagnositic studies including neuromuscular junction testing with repetitive stimulation and/or jitter studies, NCS to exclude neuropathy, and needle EMG to evaluate for myositis.	
Grading	**Management**
All Grades	All grades warrant workup and intervention given potential for progressive MG to lead to respiratory compromise
No G1	
G2: Some symptoms interfering with ADLs MGFA severity class I (ocular symptoms and findings only) and MGFA severity class II (mild generalized weakness).	• Hold ICPi and may resume in G2 patients (MGFA 1 and 2) only if symptoms resolve[8] • Should consult neurology • Pyridostigmine starting at 30 mg PO TID and gradually increase to maximum of 120mg PO QID as tolerated and based on symptoms • Administer corticosteroids (prednisone 1-1.5mg/kg orally daily) if symptoms G2. Wean based on symptom improvement.

G3-4: Limiting self-care and aids warranted, weakness limiting walking, ANY dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms. or MGFA Severity Class III-V moderate to severe generalized weakness to myasthenic crisis	• Permanently discontinue ICPi • Admit patient, may need ICU-level monitoring. • Neurology consult • Continue steroids and initiate IVIG 2G/kg IV over 5 days (0.4G/kg/day) or plasmapheresis x 5 days. • Frequent pulmonary function assessment • Daily neurological review
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 2G/kg course of IVIG over 5 days • 1-2 mg/kg methylprednisolone daily, wean based on symptom improvement • Pyridostigmine, wean based on improvement. • ICPi-associated MG may be monophasic and additional steroid sparing agents may not be required.	
7.2 Guillain-Barre Syndrome **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 Workup: • Neurologic consultation • MRI spine w/wo 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 even though this is not typically seen in classical Guillain-Barre, cytology (should be sent with any CSF sample from a patient with cancer). • Serum antibody tests for GBS variants (GQ1b for Miller Fisher variant a/w ataxia and ophthalmoplegia) • Electrodiagnostic studies to evaluate polyneuropathy • Pulmonary function testing (NIF/VC) • Frequent neurochecks	
Grading	**Management**
All grades warrant workup and intervention given potential for progressive GBS to lead to respiratory compromise. Note, there is no G1 toxicity.	
G1: Mild: None	NA
G2: Moderate: Some interference with ADLs, symptoms concerning to patient.	• Discontinue ICPi • Admission to inpatient unit with capability of rapid transfer to ICU-level monitoring • Start IVIG (0.4G/kg/day for 5 days for a total dose of 2G/kg) or plasmapheresis. Corticosteroids are usually not recommended for idiopathic GBS, however in ICPi-related forms, a trial is reasonable (methylprednisolone 2-4 mg/kg/day), followed by slow steroid taper. Pulse steroid dosing (methylprednisolone 1 gram daily for 5 days) may also be considered for G3-4 along with IVIG or plasmapheresis.
G3-4: Severe: Limiting self-care and aids warranted, weakness limiting walking, ANY dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms.	

	• Frequent neurochecks and pulmonary function monitoring. • Monitor for concurrent autonomic dysfunction • Non opioid management of neuropathic pain • Treatment of constipation/ileus
Additional Considerations: • Slow prednisone taper after steroid pulse plus IVIG or plasmapheresis • May require repeat IVIG courses • Caution with rechallenging for severe cases	
7.3 Peripheral Neuropathy **Definition:** Can present as asymmetric or symmetric sensory, motor, or sensory-motor deficit. Focal mononeuropathies including cranial neuropathies (e.g. facial neuropathies/Bell's palsy) may be present. Numbness and paresthesias may be painful or painless. Hypo- or areflexia. Sensory ataxia may be present.	
Diagnostic Workup: **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 spine w/wo contrast **G2**: In addition to above: • MRI spine advised/ MRI brain if cranial nerve • Consider EMG/NCS • Consider Neurology consultation **G3-4**: go to GBS algorithm	
Grading	**Management**
G1: Mild: No interference with function and symptoms not concerning to patient. Note: any cranial nerve problem should be managed as moderate	• Low threshold to hold ICPi and monitor symptoms for a week. If to continue, monitor very closely for any symptom progression.
G2: Moderate: Some interference with ADLs, symptoms concerning to patient (i.e. Pain but no weakness or gait limitation).	• Hold ICPi and resume once return to G1 • Initial observation OR initiate prednisone 0.5-1mg/kg (if progressing from mild) • Neurontin, pregabalin, or duloxetine for pain
G3-4: Severe: Limiting self-care and aids warranted, weakness limiting walking or respiratory problems (i.e. leg weakness, foot drop, rapidly ascending sensory changes). Severe may be GBS and should be managed as such.	• Permanently discontinue ICPi • Admit patient • Neurologic consultation • Initiate IV methylprednisolone 2-4 mg/kg and proceed as per GBS management.

7.4 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 ICPi 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 Workup:
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, parproteinemia, amyloidosis,, botulism, consider chronic diseases such as Parkinson's and other autoimmune screen
- AM orthostatic vitals
- Consider electrodiagnostic studies to evaluate for concurrent polyneuropathy
- Consider paraneoplastic LEMS, ANNA-1 ab, ganglionic acetylcholine receptor ab testing

Grading	Management
G1: Mild: No interference with function and symptoms not concerning to patient.	• Low threshold to hold ICPi and monitor symptoms for a week. If to continue, monitor very closely for any symptom progression.
G2: Moderate: Some interference with ADLs, symptoms concerning to patient	• Hold ICPi and resume once return to G1 • Initial observation OR initiate prednisone 0.5-1mg/kg (if progressing from mild) • Neurological consultation
G3-4: Severe: Limiting self-care and aids warranted	• Permanently discontinue ICPi • Admit patient • Initiate methylprednisolone 1 gram daily x 3 days followed by oral steroid taper • Neurologic consultation

7.5 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 Workup:
- MRI brain w/wo contrast + pituitary protocol
- AM cortisol, ACTH to rule out adrenal insufficiency
- Consider lumbar puncture: measure opening pressure, check cell count, protein glucose, 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

Grading	Management
G1: Mild: No interference with function and	• Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits

symptoms not concerning to patient. Note: any cranial nerve problem should be managed as moderate.	• Consider empiric antiviral (IV acyclovir) and antibacterial therapy until CSF results • 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.
G2: Moderate: Some interference with ADLs, symptoms concerning to patient (i.e. Pain but no weakness or gait limitation).	
G3-4: Severe: Limiting self-care and aids warranted	
7.6 Encephalitis **Definition:** *As for aseptic meningitis, need to exclude infectious causes, especially viral (i.e. HSV).* Confusion, altered behavior, headaches, seizures, short term memory loss, depressed level of consciousness, focal weakness, speech abnormality	
Diagnostic Workup: • Neurologic Consultation • MRI brain w/wo contrast may reveal T2/FLAIR changes typical of what is seen in autoimmune encephalopathies or limbic encephalitis or may be normal • Lumbar puncture: check cell count, protein glucose, 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 • Bloods: metabolic, 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	
Grading	**Management**
G1: Mild: No interference with function and symptoms not concerning to patient. Note: any cranial nerve problem should be managed as moderate.	• Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits • As above for aseptic meningitis suggest concurrent IV acyclovir until PCR results obtained and negative • Trial of methylprednisolone 1-2 mg/kg • If severe or progressing symptoms or oligoclonal bands present, consider pulse corticosteroids methylprednisolone 1G IV daily for 3-5 days plus IVIG 2G/kg over 5 days. • If positive for autoimmune encephalopathy antibody and limited or no improvement, consider Rituximab or plasmapheresis in consultation with neurology
G2: Moderate: Some interference with ADLs, symptoms concerning to patient (i.e. Pain but no weakness or gait limitation).	
G3-4: Severe: Limiting self-care and aids warranted	
7.7 Transverse Myelitis **Definition:** Acute or subacute weakness or sensory changes bilateral, often with increased deep tendon reflexes	

Diagnostic Workup:

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

Grading	Management
G1: Mild: No interference with function and symptoms not concerning to patient. Note: any cranial nerve problem should be managed as moderate	• Permanently discontinue ICPi • Methylprednisolone 2 mg/kg • Strongly consider higher doses of 1G/day for 3-5 days • Strongly consider IVIG
G2: Moderate: Some interference with ADLs, symptoms concerning to patient (i.e. Pain but no weakness or gait limitation).	
G3-4: Severe: Limiting self-care and aids warranted	

8.0 AUTOIMMUNE HEMATOLOGIC TOXICITY

8.1 Hemolytic Anemia

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

Diagnostic Workup:

- 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 includePTNIR, infectious causes
- Autoimmune serology
- PNH screening
- Direct and indirect bilirubin, LDH, direct agglutinin test, and if no obvious cause, bone marrow analysis, cytogenetic analysis to evaluate MDS
- Evaluation for viral/bacterial (mycoplasma etc.) causes of hemolysis studies
- Protein electrophoresis, cryoglobulin analysis
- Workup for BM failure syndrome if refractory including B12, folate, copper, parvo virus, FE, thyroid, infectious
- Glucose-6-phosphate dehydrogenase
- Evaluation of common drug causes (ribavirin, rifampin, dapsone, interferon, cephalosporins, penicilllins, NSAIDS, Quinine/quinidine, fludarabine, ciprofloxacin, lorazepam, diclofenac etc)
- Assessment of methemaglobinemia

Grading	Management
G1: Hgb<LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	• Continue ICPi with close clinical follow-up and laboratory evaluation
G2: Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	• Hold ICPi and strongly consider permanent discontinuation • Administer 0.5 to 1 mg/kg/day prednisone equivalents
G3: Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	• Permanently discontinue ICPi • Should use clinical judgement and consider admitting the patient • Hematology consult • Prednisone 1-2 mg/kg/day (oral or IV depending on symptoms/speed of development) • If worsening or no improvement, 1 to 2 mg/kg/day prednisone equivalents and permanently discontinue ICPi treatment • 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 hemoglobin range (7 to 8 g/dL in stable, non-cardiac in-patients) • Should offer patients supplementation with folic acid 1mg QD
G4: Life-threatening consequences; urgent intervention indicated	• Permanently discontinue ICPi • Admit patient • Hematology consult • IV prednisone corticosteroids 1-2 mg/kg/day • If no improvement on or if worsening on corticosteroids or severe symptoms on presentation, initiate other immunosuppressive drugs, such as rituximab, IVIG, CSA, infliximab, MMF and ATG • RBC transfusion per existing guidelines. Discuss with blood bank team prior to transfusions that a patient with possible ICPi SAE is in house.
Additional Considerations: • Monitor hemoglobin levels on a weekly basis until the steroid tapering process is complete. Thereafter, less frequent testing is needed.[9]	
8.2 Acquired Thrombotic thrombocytopenic purpura **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 (e.g. chemotherapy, sirolimus, tacrolimus, opana ER antibiotics, quinine,) • Physical exam, peripheral smear • ADAMTS13 activity level and inhibitor titer • LDH, haptoglobin, reticulocyte count, bilirubin, urinalysis to rule out other causes • Prothrombin time, activated partial thromboplastin time, fibrinogen • Blood group and antibody screen, direct antiglobulin test, cytomegalovirus serology • Consider CT/MRI brain, echocardiogram, electrocardiogram	

- Viral studies
- Note: this disorder is usually associated with severe drop in platelets and hemolysis/anemia precipitously

Grading	Management
All Grades	• 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. • Initially, the patient should be stabilized and any critical organ dysfunction stabilized.
G1: Evidence of RBC destruction (schistocytosis) without anemia, renal insufficiency or thrombocytopenia clinically	• Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits, noting that there is currently no data to recommend restarting ICPi therapy • Hematology consult • Administer 0.5 to 1 mg/kg/day prednisone
G2: Evidence of RBC destruction (schistocytosis) without clinical consequence with G2 anemia and thrombocytopenia	
G3: Laboratory findings with clinical consequences (G3 thrombocytopenia, anemia, renal insufficiency >2)	• Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits, noting that there is currently no data to recommend restarting ICPi therapy • Hematology consult • In conjunction with hematology Initiate PEX according to existing guidelines with further PEX dependent on clinical progress[10-12] • Administer methylprednisolone 1 g intravenously daily for 3 days, with the first dose typically administered immediately after the first PEX • May offer rituximab
G4: Life-threatening consequences, (e.g., CNS hemorrhage or thrombosis/embolism or renal failure)	

8.3 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 PE (special consideration for new history of high risk drugs, HTN 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/MMA
- 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

Grading	Management
G1-2: Evidence of RBC destruction (schistocytosis) without clinical consequences of anemia, thrombocytopenia grade II	• Continue ICPi with close clinical follow-up and laboratory evaluation • Supportive care
G3: Laboratory findings with clinical consequences (e.g., renal insufficiency, petechiae)	• Permanently discontinue ICPi • Begin therapy with Eculizumab therapy 900mg weekly x 4 doses, 1200mg week 5, then 1200mg every two weeks. • Red blood transfusion according to existing guidelines
G4: Life-threatening consequences, (e.g., CNS thrombosis/embolism or renal failure)	

8.4 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
- W/u for infectious causes.
- Identify marrow hypo/aplasia
- BM biopsy and BM 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	
Grading	**Management**
G1: nonsevere: >0.5 polymorphonuclear cells (PMNs) × 10^9/L hypocellular marrow, with marrow cellularity<25%, Peripheral platelet count >20,000, reticulocyte count >20,000	• Hold ICPi, provide growth factor support and close clinical follow-up and laboratory evaluation. Supportive transfusions as per local guidelines. • Supportive transfusions as per local guidelines
G2: severe: Hypocellular marrow <25% and tow of the following ANC <500, peripheral platelet <20,000 and Reticulocyte <20,000	• Hold ICPi and provide growth factor support and close clinical laboratory evaluations daily • Administer ATG + Cyclosporine. HLA typing and evaluation for bone marrow transplantation if patient is candidate. All blood products should be irradiated and filtered. • Supportive care with GCSF may be added in addition
G3-4: very severe: ANC<200, platelet count <20,000, reticulocyte count of <20,000, plus hypocellular marrow <25%.	• Hold ICPi and monitor weekly for improvement. If not resolved, discontinue treatment until AE has reverted to grade 1 • Hematology consult, growth factor support • Horse ATG plus cyclosporine • If no response, repeat immunosuppression with Rabbit ATG plus cyclosporine, cyclophosphamide • For refractory patients consider eltrombopag plus supportive care
8.5 Lymphopenia **Definition:** An abnormally low level of lymphocytes in peripheral blood (PB); for adults, counts of less than 1,500/mm^3	
Diagnostic Workup: • History and physical exam (special attention for lymphocyte depleting therapy such as Fludarabine, ATG, steroids, cytotoxic chemotherapy, radiation exposure etc s 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	
G1-2: 500-1000 PB lymphocyte count	• Continue ICPi
G3: 250-499 PB lymphocyte count	• Continue ICPi, checking CBC weekly for monitoring, initiation of CMV screening
G4: <250 PB lymphocyte count	• Consider holding ICPi • Initiate *Mycobacterium avium* complex prophylaxis and *Pneumocystis jirovecii* prophylaxis, CMV screening. HIV/Hepatitis screening if not already done. • May consider EBV testing if evidence of lymphadenopathy/hepatitis, fevers, hemolysis occur c/w lymphoproliferative disease occurs
8.6 Immune thrombocytopenia (ITP) **Definition:** an autoimmune disorder characterized by immunologic destruction of otherwise normal platelets	
Diagnostic Workup:	

<table>
<tr><td colspan="2">• History and physical examination (special attention for lymphocyte depleting therapy such as Fludarabine, ATG, steroids, cytotoxic therapy)
• FH 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's syndrome
• Nutritional evaluation
• BM evaluation if other cell lines affected and concern for aplastic anemia</td></tr>
<tr><th>Grading</th><th>Management</th></tr>
<tr><td>G1: Platelet count <100/uL</td><td>• Continue ICPi with close clinical follow-up and laboratory evaluation</td></tr>
<tr><td>G2: Platelet count <75/uL</td><td>• Hold ICPi, but monitor for improvement. If not resolved, interrupt treatment until AE has reverted to Grade 1
• Administer prednisone 1 mg/kg per day (dosage range, 0.5–2 mg/kg per day) orally for 2-4 weeks after which time this medication should be tapered over 4-6 weeks to the lowest effective dose
• IVIG may be used in conjunction with corticosteroids if a more rapid increase in platelet count is required.</td></tr>
<tr><td>G3: Platelet count <50/uL</td><td rowspan="2">• Hold ICPi, but monitor for improvement. If not resolved, interrupt treatment until AE has reverted to Grade 1
• Hematology consult
• Prednisone corticosteroids 1-2 mg/kg/day (oral or IV depending on symptoms)
• If worsening or no improvement, 1 to 2 mg/kg/day prednisone equivalents and permanently discontinue treatment
• IVIG be used with corticosteroids when a more rapid increase in platelet count is required
• If IVIG is used, the dose should initially be 1 g/kg as a one-time dose. This dosage may be repeated if necessary
• If previous treatment with corticosteroids and/or, IVIG, has been unsuccessful, subsequent treatment may include rituximab, thrombopoietin receptor agonists, or more potent immunosuppression
(From American Society of Hematology guideline on immune thrombocytopenia[13] – consult for further details)</td></tr>
<tr><td>G4: Platelet count <25/uL</td></tr>
<tr><td colspan="2">8.7 Acquired Hemophilia
Definition: disorder caused by the development of autoantibodies (inhibitors) directed against plasma coagulation factors,</td></tr>
<tr><td colspan="2">Diagnostic Workup:
• Full blood count to assess platelet number, fibrinogen, PT, PTT, INR. The typical finding in patients with AHA is a prolonged aPTT with a normal prothrombin time (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</td></tr>
<tr><th>Grading</th><th>Management</th></tr>
<tr><td>G1: Mild: 5-40% of normal factor activity in blood; 0.05-0.4 IU/ml of whole blood</td><td>• Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits
• Administer 0.5 to 1 mg/kg/day prednisone
• Transfusion support as required</td></tr>
</table>

	• Treatment of bleeding disorders with hematology consult
G2: Moderate: 1-5% of normal factor activity in blood; 0.01-0.05 IU/ml of whole blood	• Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits • Hematology consult • Administration of factor replacement (choice based on BU of titer) • Administer 1 mg/kg/day prednisone ± rituximab (dose 375mg/m2 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. • Factors should be provided to increase level during bleeding episodes, with choice of factor based on presence or absence of inhibitor
G3-4: Severe: <1% of normal factor activity in blood; < 0.01 IU/ml of whole blood	• Permanently discontinue ICPi • Admit patient • Hematology consult • Administration of factor replacement, choice based on BU level of inhibitor. • Bypassing agents may be used (Factor VII FEIBA). Caution should be taken in elderly and those with CAD • Prednisone corticosteroids 1-2 mg/kg/day (oral or IV depending on symptoms)± rituximab (dose 375mg/m2 weekly x 4 weeks) and/or cyclophosphamide (dose 1-2mg/kg/day). • Transfusion support as required for bleeding • If worsening or no improvement add, cyclosporine, or immunosuppression/immunoadsorption
Additional Considerations: • AHA 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.[14]	
9.0 CARDIOVASCULAR TOXICITY	
9.1 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 Workup: 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 catherization
- Cardiac MRI

Grading	Management
G1: Abnormal cardiac biomarker testing, including abnormal ECG	All grades warrant workup and intervention given potential for cardiac compromise
G2: Abnormal screening tests with mild symptoms	Please consider the following: • Hold ICPi and permanently discontinue after G1 • High-dose corticosteroids (1-2 mg/kg of prednisone) initiated rapidly (oral or IV depending on symptoms). • Admit patient, cardiology consultation • Management of cardiac symptoms according to ACC/AHA guidelines and with guidance from cardiology • Immediate transfer to a coronary care unit should be considered for patients with elevated troponin or conduction abnormalities. • 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
G3: Moderately abnormal testing or symptoms with mild activity	
G4: Moderate to severe decompensation, intravenous medication or intervention required, life threatening conditions	

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. [15]

9.2 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 Workup:

Evaluation of signs and symptoms of PE or DVT may include:
- Clinical prediction rule to stratify patients with suspected VTE
- Venous US 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
- V/Q scan is also an option when CTPA is not appropriate
- Consider other testing, including ECG, chest radiography, BNP and troponin levels, and ABG

Grading	Management
G1: Venous thrombosis (e.g., superficial thrombosis)	• Continue ICPi • Warm compress • Clinical surveillance

G2: Venous thrombosis (e.g., uncomplicated deep vein thrombosis), medical intervention indicated	• Continue ICPi • Management according to CHEST, ACC and/or AHA guidelines and consider consult from cardiology or other relevant specialties • LMWH is suggested over VKA, dabigatran, rivaroxaban apixaban, or edoxaban for initial and long-term treatment • IV heparin is an acceptable alternative for initial use and oral anticoagulants are acceptable for the long term
G3: Thrombosis (e.g., uncomplicated pulmonary embolism [venous], non-embolic cardiac mural [arterial] thrombus), medical intervention indicated	
G4: Life-threatening (e.g., pulmonary embolism, cerebrovascular event, arterial insufficiency); hemodynamic or neurologic instability; urgent intervention indicated	• Permanently discontinue ICPi • Admit patient and management according to CHEST, ACC and/or AHA guidelines and with guidance from cardiology • Respiratory and hemodynamic support • LMWH is suggested over VKA, dabigatran, rivaroxaban, apixaban, or edoxaban for initial and long-term treatment • IV heparin is an acceptable alternative for initial use and oral anticoagulants are acceptable for the long term • Further clinical management as indicated based on symptoms

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 ICPi 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 ICPi 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.[16,17]

10.0 OCULAR TOXICITY

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	
10.1 Uveitis/Iritis **Definition:** Inflammation of the middle layer of the eye	
Diagnostic Workup: As per 10.0	
Grading	**Management**
G1: Asymptomatic	• Continue ICPi • Refer to ophthalmology within 1 week • Artificial Tears
G2: Medical Intervention required, anterior uveitis	• Hold ICPi temporarily until after ophthalmology consult • Urgent Ophthalmology referral • Topical corticosteroids, cycloplegic agents, systemic corticosteroids • May resume ICPi treatment once off systemic steroids which are purely indicated for ocular side effect or once corticosteroids for other concurrent systemic irAE are reduced to ≤10mg. Continued topical/ocular steroids are permitted when resuming therapy to manage and minimize local toxicity • Retreat after return to ≤ G1
G3: Posterior or pan-uveitis	• Permanently discontinue ICPi • Urgent ophthalmology referral. • Systemic corticosteroids and intravitreal/periocular/topical corticosteroids
G4: 20/200 or worse	• Permanently discontinue ICPi • Emergent ophthalmology referral. • Systemic corticosteroids - IV prednisone 1-2mg/kg or methylprednisolone 0.8-1.6mg/kg and intravitreal/periocular/topical corticosteroids per ophthalmologist opinion
Additional Considerations: Consider use of infliximab or other TNFa blockers in cases that are severe and refractory to standard treatment. [18,19]	
10.2 Episcleritis **Definition:** Inflammatory condition affecting the episcleral tissue between the conjunctiva and the sclera that occurs in the absence of an infection	
Diagnostic Workup: As per 10.0	

Grading	Management
G1: Asymptomatic	• Continue ICPi • Refer to ophthalmology within 1 week • Artificial Tears
G2: vision 20/40 or better	• Hold ICPi therapy temporarily until after ophthalmology consult • Urgent ophthalmology referral • Topical corticosteroids, cycloplegic agents, systemic corticosteroids
G3: Symptomatic and vision worse than 2/40	• Permanently discontinue ICPi • Urgent ophthalmology referral. • Systemic corticosteroids and topical corticosteroids with cycloplegic agents
G4: 20/200 or worse	• Permanently discontinue ICPi • Emergent ophthalmology referral. • Systemic corticosteroids and topical corticosteroids with cycloplegic agents
Additional Considerations: Consider use of infliximab or other TNFa blockers in cases that are severe and refractory to standard treatment. [18,19]	
10.3 Blepharitis **Definition:** Inflammation of the eyelid that affects the eyelashes or tear production	
Diagnostic Workup: As per 10.0	
Grading	**Management**
No formal grading system	• Warm compresses and lubrication drops • Continue therapy unless persistent and serious

Abbreviations: ACC, American College of Cardiology; **AChR**, acetylcholine receptor; **ACTH**, adrenocorticotropic hormone; **ADL**, activities of daily living; **AE**, adverse event; **AHA**, American Heart Association; **AKI**, acute kidney injury; **ANA**, antinuclear antibody; **ANC**, antineutrophil cytoplasmic antibodies; **ANCA**, antineutrophil cytoplasmic antibodies; **ATG**, antithymocyte globulin; **BAL**, bronchoalveolar lavage; **BNP**, brain natriuretic peptide; **BSA**, body surface area; **CCP**, citrullinated protein antibody; **CK**, creatine kinase; **CMV**, cytomegalovirus; **CPK**, creatine phosphokinase; **CRP**, C-reactive protein; **CT**, computed tomography; **CTCAE**, Common Terminology Criteria for Adverse Events; **CTLA-4**, cytotoxic T-cell lymphocyte-4; **CTPA**, computed tomography pulmonary angiography; **CXR**, chest x-ray; **DIC**, disseminated intravascular coagulation; **DIHS**, drug-induced hypersensitivity syndrome; **DKA**, diabetic ketoacidosis; **DLCO**, diffusing capacity of lung for carbon monoxide; **DM**, diabetes mellitus; **DMARD**, disease-modifying antirheumatic drug; **DRESS**, drug reaction with eosinophilia and systemic symptoms; **DVT**, deep vein thrombosis; **EBV**, Epstein-Barr virus; **EGD**, esophagogastroduodenoscopy; **EMG**, electromyography; **EMS**, emergency medical services; **ESR**, erythrocyte sedimentation rate; **FSH**, follicle-stimulating hormone; **FT4**, free thyroxine; **G**, grade; **GPI**, glycosylphosphatidylinositol; **Hgb**, hemoglobin; **HHV6**, human herpesvirus 6; **HIV**, human immunodeficiency virus; **HSV**, herpes simplex virus; **ICPi**, immune checkpoint inhibitor; **ICU**, intensive care unit; **IgG**, immunoglobulin G; **IL**, interleukin; **INR**, international normalized ratio; **irAE**, immune-related adverse event; **IV**, intravenous; **IVIG**, intravenous immunoglobulin; **LDH**, lactate dehydrogenase; **LH**, luteinizing hormone; **LLN**, lower limit of normal; **LMWH**, low-molecular-weight heparin; **MGFA**, Myasthenia Gravis Foundation of America; **MRI**, magnetic resonance imaging; **NA**, not applicable; **NCS**, nerve conduction study; **NIF**, negative inspiratory force; **NSAID**, nonsteroidal anti-inflammatory drug; **PB**, peripheral blood; **PCP**, *Pneumocystis* pneumonia; **PCR**, polymerase chain reaction; **PD-1**; programmed death 1; **PD-L1**, programmed death ligand 1; **PE**, pulmonary embolism; **PEX**, plasma exchange; **PNH**, paroxusmal nocturnal hemoglobinuria; **PPI**, proton pump inhibitor; **PT**, prothrombin time; **PTT**, partial thromboplastin time; **PTU**, propylthiouracil; **RF**, rheumatoid factor; **RPR**, rapid plasma reagin, **SCAR**, severe cutaneous adverse reactions; **SJS**, Stevens-Johnson syndrome; **SSKI**, potassiumiodide; **T1DM**, type 1 diabetesmellitus; **T2DM**, type 2 diabetesmellitus; **TB**, tuberculosis; **TNF**, tumor necrosis factor; **TENS**, toxic epidermal necrolysis; **TPO**, thyroid peroxidase; **TRAb**, thyroid-stimulating hormone receptor antibody; **TSH**, thyroid-stimulating hormone; **TSI**, thyroid-stimulating immunoglobulin; **TTE**, transthoracic echocardiogram; **TTP**, thrombotic thrombocytopenic purpura; **ULN**, upper limit of normal; **UTI**, urinary tract infection; **VC**, vital capacity; **VKA**, vitamin K agonist

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