## Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update

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1.0. Cutaneous Toxicities

1.1. Rash or Inflammatory Dermatitis

**Workup and Evaluation:**
- Pertinent history and physical exam including examination of the oral mucosa, assessment for blister formation, assessment of body surface area involved.
- Review full list of patient medications to rule out other drug-induced cause for photosensitivity.
- Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, including prior or other recent cancer therapies, or a skin condition linked to another systemic disease or unrelated primary skin disorder.
- Recent or new complete blood count and comprehensive metabolic panel (if needed for skin differential diagnosis).
- Consider referral to dermatologist if autoimmune skin disease is suspected.
- Consider skin biopsy.
- Consider clinical monitoring with use of serial clinical photography.

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

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<th>G1: Rash covering &lt;10% BSA, which may or may not be associated with symptoms of pruritus or tenderness.</th>
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<tr>
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<td>Continue ICPi.</td>
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<td>Treat with topical emollients and/or mild-moderate potency topical corticosteroids.</td>
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<td>Counsel patients to avoid skin irritants.</td>
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<th>Management</th>
<th>G2: Rash covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental activities of daily living (ADL); rash covering &gt; 30% BSA with or without mild symptoms.</th>
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<td>Consider holding ICPi and monitor weekly for improvement. If skin toxicity not improved after 4 weeks, then re-grade toxicity as grade 3.</td>
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<td>In addition, treat with topical emollients, oral antihistamines, and medium-to-high potency topical corticosteroids.</td>
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<td>Consider initiating prednisone (or equivalent) at dosing 0.5-1 mg/kg, tapering over 4 weeks. In patients with pruritis without rash, consider topical anti-itch remedies (e.g. refrigerated menthol, pramoxine).</td>
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<th>G3: Rash covering &gt;30% BSA with moderate or severe symptoms; limiting self-care ADL.</th>
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<td>Hold ICPi therapy and consult with dermatology to determine appropriateness of resuming.</td>
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<td>Treat with topical emollients, oral antihistamines, and high-potency topical corticosteroids. May also consider phototherapy to treat severe pruritus.</td>
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<td>Initiate oral prednisone or equivalent (1 mg/kg/d) tapering over at least 4 weeks.</td>
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<td>Once downgraded to ≤G1 and prednisone (or equivalent) below 10mg/d, clinicians may consider resuming ICPi therapy with close monitoring and follow-up with dermatology in certain cases such as psoriasis.</td>
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<td>In patients with pruritis without rash, may treat with gabapentin, pregabalin, aprepitant, or dupilumab.</td>
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### 1.0. Cutaneous Toxicities

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<th>Grade 4 (G4): Severe consequences requiring hospitalization or urgent intervention indicated or life-threatening consequences.</th>
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<td>• Immediate hold ICPI</td>
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<td>• May admit patient immediately with direct oncology involvement and with an urgent consult by dermatology.</td>
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<td>• Systemic steroids: IV methylprednisolone (or equivalent) dosed at 1-2mg/kg with slow tapering when the toxicity resolves.</td>
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<tr>
<td>• Monitor closely for progression to Severe Cutaneous Adverse Reaction (SCAR).</td>
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<td>• Consider alternative antineoplastic therapy over resuming ICPIs if the skin irAE does not resolve to ≤G1. If ICPIs are the patient’s only option, consider restarting once these side effects have resolved to a G1 level with close dermatology follow-up.</td>
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### 1.2. Bullous Dermatoses

**Workup and Evaluation:**
- 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.
- Dermatology consultation for consideration of skin biopsy and direct immunofluorescence. Further serologic work-up, such as ELISA testing or indirect immunofluorescence may be pursued.
- Primer on monitoring for complicated cutaneous adverse drug reactions:
  - Review of systems: Skin pain (“like a sunburn”), fevers, malaise, myalgias, arthralgias, abdominal pain, ocular discomfort or photophobia, sores or discomfort in the nares, sores or discomfort in the oropharynx, odynophagia, hoarseness, dysuria, sores or discomfort in the vaginal area for women or involving the meatus of the penis for men, sores in the perianal area or pain with bowel movements.
  - Physical exam: Include vital signs and a full skin exam specifically evaluating all skin surfaces and mucous membranes (eyes, nares, oropharynx, genitals, and perianal area). Assess for lymphadenopathy, facial or distal extremity swelling (may be signs of DIHS/DRESS (see 1.3 Section). Assess for pustules or blisters or erosions in addition to areas of “dusky erythema” which may feel painful to palpation.

<table>
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<th>Grading</th>
<th>Management</th>
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<td><strong>G1:</strong> Asymptomatic or blisters covering &lt;10% BSA and no associated erythema</td>
<td>• If blisters are &lt;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.</td>
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<td>• When symptomatic bullae or erosions, which are “deroofed” vesicles or bullae, are noted on the skin or mucosal surfaces, the cutaneous irAE is considered at least grade 2.</td>
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<td>• See grade 2 management recommendations.</td>
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<td><strong>G2:</strong> Blistering that affects quality of life and require intervention based on diagnosis not meeting criteria for &gt; grade 2. Blister covering 10%-30% BSA.</td>
<td>• Hold ICPI therapy and consult with dermatology for steroid-sparing options, work up, and to determine appropriateness of resuming.</td>
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<td>• 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 on the skin after the blister has “popped” or if the roof of the blister easily sloughs off.</td>
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<td>• Initiate class 1 high potency topical steroid, e.g. clobetasol, betamethasone, or equivalent and reassess every 3 days for progression or improvement.</td>
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<td>• Low threshold to initiate treatment with prednisone (or equivalent) at 0.5-1 mg/kg/d dosing and taper over at least 4 weeks.</td>
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<td>• Monitor patients closely for progression to greater body surface area involvement and/or mucous membrane involvement. Consider following patients closely using serial photography.</td>
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<tr>
<td>Grade</td>
<td>Description</td>
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| G3    | Skin sloughing covering >30% BSA with associated pain and limiting self-care ADL.                                                                     | Hold ICPI therapy and consider admitting patient.  
  - Administer IV methylprednisolone (or equivalent) 1-2 mg/kg and when appropriate convert to oral steroids, tapering over at least 4 weeks.  
  - If bullous pemphigoid is diagnosed, it may be possible to avoid long-term use of systemic steroids and transition to steroid-sparing options (e.g., IVIG and rituximab), as an alternative approach to treating the irAE.  
  - Consult with dermatology to determine appropriateness of resuming ICPI once symptoms improve. |
| 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) 1–2 mg/kg and when appropriate convert to oral steroids, tapering over at least 4 weeks.  
  - If bullous pemphigoid is diagnosed, it may be possible to avoid long-term use of systemic steroids and treat with steroid-sparing options, as an alternative approach to treating the irAE (e.g., IVIG and rituximab). |

### 1.3. Severe Cutaneous Adverse Reactions (SCAR)

**Workup and Evaluation:**
- 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 CBC with DIFF, liver and kidney function tests; consider UA in the context of DRESS to assess for associated nephritis 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 or TEN, as well as other possible etiologies like paraneoplastic pemphigus or other autoimmune blistering dermatoses or other drug reactions, such as AGEP.
- Follow 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.
- Follow primer on monitoring for complicated cutaneous adverse drug reactions from section 1.2.

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<th>All Grades</th>
<th>In cases of suspected SJS or any mucous membrane involvement (not including isolated stomatitis), discontinue ICPI treatment and consult dermatology. Monitor closely for improvement regardless of grade.</th>
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<td>G1 and G2</td>
<td>For the SCAR adverse reactions, there are no grade 1 or 2 categories. If limited body surface area is involved with bullae or erosions, there should remain high concern that this reaction will progress to grade 3 or 4.</td>
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### 1.0. Cutaneous Toxicities

| Grade 3 (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.  
Admit to burn unit and/or consult wound services with attention to supportive care including fluid and electrolyte balance, minimizing insensible water losses, and preventing infection.  
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.  
Given the immune mechanism of action of these medicines, use of immune suppression is warranted and should be offered. The usual prohibition of corticosteroids for SJS is not relevant here, as the underlying mechanism is a T-cell immune-directed toxicity. Adequate suppression is necessary with corticosteroids or other agents and may be prolonged in cases of DRESS or drug hypersensitivity syndrome.  
For mucous membrane involvement of SJS or TEN, appropriate consulting services should be offered to guide management in preventing sequelae from scarring (e.g. ophthalmology, otolaryngology, urology, or gynecology, as appropriate). |
| Grade 4 (G4): Skin erythema and blistering/sloughing covering ≥10% BSA with associated signs (e.g., erythema, purpura, epidermal detachment, mucous membrane detachment) and/or systemic symptoms and concerning associated blood work abnormalities (e.g., liver function test elevations in the setting of DRESS or 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. ophthalmology, urology, gynecology, otolaryngology, 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. |

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2.0. Gastrointestinal Toxicities

2.1. Colitis

Workup and Evaluation:

G2:
- Work up of blood (CBC, CMP, TSH), stool (culture, *C. diff*, parasite, CMV or other viral etiology, O&P if appropriate), should be performed for the initial presentation, and also considered for immunosuppressant refractory cases.
- Consider testing for fecal 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 TB testing), repeated annually in patients who require biologic treatment e.g. infliximab or vedolizumab for >1 year until treatment is completed.
- Consider reviewing concomitant medications that could alter the gut microbiome and their indications for prolonged use (e.g. proton pump inhibitors, antibiotics, and probiotics).
- Imaging, e.g., CT scan of abdomen and pelvis for colitis-related symptoms (abdominal pain, bleeding) to rule out colitis-related complications, including typhlitis and bowel perforation/abscess.
- GI endoscopy/Colonoscopy with biopsy for patients who have positive stool inflammatory markers or colitis-related symptoms 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.
- Repeat colonoscopy may be considered for cases grade ≥ 2 for disease activity monitoring to document complete remission, especially if there is a plan to resume ICPI. Mucosal healing on repeat endoscopy and/or fecal calprotectin level ≤ 116µg/g can be considered the treatment target to guide decisions on when to stop biologic treatment and when to resume ICPI therapy.1-3

G3-4:
- Complete all recommendations as above and consider inpatient care.

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<th>Grading (based on CTCAE for diarrhea, as most often used clinically)</th>
<th>Management</th>
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| 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, constipation.  
For grade ≥ 2, consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patients recover to ≤ G1; 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 G1 or resolves.  
May also include supportive care with medications such as loperamide if infection has been ruled out in patients with diarrhea only and not colitis-related symptoms as a temporary measure.  
Monitor for dehydration and recommend dietary changes.  
Patient should be closely monitored by phone or electronic medical system for symptoms changes by clinical providers every 3 days or more frequently if needed until stabilized.  
May obtain gastroenterology consult for prolonged G1 cases and consider endoscopy with biopsies. |
### 2.0. Gastrointestinal Toxicities

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<th>Description</th>
<th>Management Strategies</th>
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| **G2**: Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline | - Hold ICPI at least until recovery to G1 – see last bullets.  
- May also include supportive care with medications such as loperamide if infection has been ruled out in patients with diarrhea only and not colitis-related symptoms as a temporary measure.  
- Consider consult with gastroenterology for ≥G2.  
- Administer corticosteroids, unless diarrhea is transient, starting with initial dose of 1 mg/kg/d prednisone or equivalent until symptoms improve to G1, and then start taper over 4-6 weeks.  
- Consider adding narrower-spectrum/more potent agents, including anti-tumor necrosis factor (infliximab) or anti-integrin (vedolizumab) antibody to patients whose colitis is corticosteroid-refractory (i.e. no decrease by one grade in 72 hours) or dependent or with high-risk endoscopic features* on initial endoscopy exam.  
- When symptoms improve to ≤G1, taper corticosteroids over 4-6 weeks; may consider shorter tapers in patients also treated with biologics.  
- Endoscopic evaluation with EGD/colonoscopy is highly recommended for cases grade ≥ 2 to stratify patients for early treatment of biologics based on the endoscopic findings.  
- Resuming ICPI after symptoms improve to ≤G1 may be considered when steroid taper is completed, risk/benefits reviewed if maintained on biologics, and/or if endoscopic and histologic remission are achieved. Fecal calprotectin <116 μg/g may be considered as a surrogate for endoscopic and histologic remission.  
- Resuming PD-1/PD-L1 agent is associated with lower risk of flare-up, however, CTLA-4 inhibitor can still be considered in selected cases, such as in patients who have not yet responded or whose response is deemed inadequate. |  |
| **G3**: Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL | - Follow G2 recommendations as listed, with the following additions for G3:  
- Administer corticosteroids (initial dose of 1 to 2 mg/kg/d prednisone or equivalent) until symptoms improve to G1, and then start taper over 4-6 weeks. Consider IV methylprednisolone, especially if concern for concurrent upper GI inflammation.  
- Consider early introduction of infliximab or vedolizumab in addition to steroids in patients with high-risk endoscopic features* on initial endoscopy exam or inadequate response to steroids (persistent symptoms after 3 days).  
- Consider hospitalization for patients with dehydration or electrolyte imbalance.  
- Consider repeat colonoscopy in patients who are immunosuppression-refractory.  
- Should consider permanently discontinuing CTLA-4 agents. |  |
| **G4**: Life-threatening consequences; urgent intervention indicated | - Follow G2-G3 recommendations as listed, with the following additions for G4:  
- Permanently discontinue treatment.  
- Should provide inpatient care.  
- Administer 1 to 2 mg/kg/d methylprednisolone or equivalent until symptoms improve to G1, and then start taper over 4-6 weeks.  
- Consider early biologics (infliximab or vedolizumab) if inadequate response to steroids after 3 days.  
- Consider lower GI endoscopy if symptoms are refractory despite treatment or there is concern of new infections. |  |
2.0. Gastrointestinal Toxicities

Additional Considerations:
- May consider fecal microbiota transplant, JAK inhibitor tofacitinib or IL-12 blocking antibody ustekinumab in patients who are refractory to the previous immunosuppressants.
- Patients with both irAE-related hepatitis and irAE-related colitis are less common, and management may include permanently discontinuing ICPI and offering other immunosuppressant agents (e.g., prednisone and mycophenolate) that work systemically for both conditions. Infliximab is contraindicated for hepatic irAE.
- Currently, enteritis and/or gastritis alone as the cause of gastrointestinal toxicity is uncommon and endoscopy with biopsy is recommended as the evaluation tool. It may be managed similarly to colitis including steroid and/or biologics etc.

2.2. Hepatitis

Workup and Evaluation:
- Monitor patient for abnormal liver blood tests: AST, ALT, and bilirubin prior to each infusion and/or consider weekly if grade 1 LFT elevations. No treatment is recommended for grade 1 LFT abnormality.
- Review medications and supplements that may cause hepatotoxicity and rule out abnormal liver enzymes from development or progression of liver metastases.
- Liver biopsy should be considered if the patient is steroid refractory or if concern for other differential diagnoses that would alter medical management.

For grade ≥2:
- Work up for other causes of elevated liver enzymes (e.g. viral hepatitis, alcohol history, iron studies, thromboembolic event, or potential liver metastasis from primary malignancy) by doing blood work and imaging (ultrasound and cross-sectional imaging). 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 CK for other etiologies.

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| G1: Asymptomatic (AST or ALT >ULN to 3.0× ULN and/or total bilirubin >ULN to 1.5× ULN) | • Continue ICPI with close monitoring; consider alternate etiologies.  
• Consider monitoring labs 1 to 2 times weekly.  
• Manage with supportive care for symptom control. |
| G2: Asymptomatic (AST or ALT >3.0 to ≤5× ULN and/or total bilirubin >1.5 to ≤3× ULN) | • Hold ICPI temporarily.  
• Patients should be advised to stop unnecessary medications and any known hepatotoxic drugs. Temporarily hold other potentially hepatotoxic oncologic agents.  
• For grade 2 hepatic toxicity, may administer steroid (0.5-1mg/kg day prednisone) or equivalent if no improvement is seen after 3-5 days.  
• Increase frequency of monitoring to every 3 days.  
• If inadequate improvement after 3 days, consider adding mycophenolate mofetil.  
• May initiate steroid taper when symptoms improve to ≤ G1 and may resume ICPI treatment when steroid ≤ 10mg/d. Taper over at least 1 month.  
• Consider hepatology consult for G2 and above.  
• May resume if recover to ≤ G1 on prednisone ≤ 10mg/d. |
## 2.0. Gastrointestinal Toxicities

| G3: AST or ALT 5-20× ULN and/or total bilirubin 3-10× ULN, OR symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis; reactivation of chronic hepatitis | Follow G2 recommendations as listed, with the following additions for G3:  
   - Consider permanently discontinuing ICPI if asymptomatic; permanently discontinue if symptomatic.  
   - Immediately start steroid 1-2 mg/kg methylprednisolone or equivalents.  
   - If steroid refractory, consider liver biopsy to rule out NASH, tumor, cholestatic variants, other drug-related hepatic inflammation, infection, or other autoimmune entity and consider adding azathioprine\(^B\) or mycophenolate\(^C\) if infectious cause is ruled out.  
   - Labs daily or every other day; consider inpatient monitoring for patients with AST/ALT > 8 × ULN and/or elevated total bilirubin 3 × > ULN.  
   - If no improvement is achieved with steroid or for patients on ICPI therapy combined 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 when ≤ G1, re-escalate if needed, optimal duration unclear.  
   - Consider transfer to tertiary care facility if necessary. |
|---|---|
| G4: AST or ALT >20× ULN and/or total bilirubin >10× ULN OR decompensated liver function (e.g., ascites, coagulopathy, encephalopathy, coma) | Follow G3 recommendations as listed, with the following additions for G4:  
   - Administer 2 mg/kg/d methylprednisolone equivalents. |

### Additional considerations:

- Infliximab is contraindicated for immune-related hepatitis.

\(^A\) High-risk endoscopic features include large deep ulceration, multiple ulcers, and extensive colitis beyond left colon.\(^1,2\)

\(^B\) Anecdotal experience suggests azathioprine may be beneficial in steroid-refractory immune-related hepatitis. If using azathioprine, should test for thiopurine methyltransferase (TPMT) deficiency.

\(^C\) A case study reports use of mycophenolate mofetil in steroid-refractory immune-related hepatitis with some success.\(^8\)
## 3.0. Lung Toxicities

### 3.1. Pneumonitis

#### Workup and Evaluation
- Should include the following: Pulse oximetry, CT chest preferably with contrast if concerned for other etiologies such as pulmonary embolus.
- For G2 or higher, may include the following infectious workup: nasal swab, sputum culture, and sensitivity, blood culture and sensitivity, urine culture, and sensitivity.
- COVID-19 evaluation – per institutional guidelines where relevant.

<table>
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<tr>
<th>Grading</th>
<th>Management</th>
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| G1: Asymptomatic; confined to one lobe of the lung or < 25% of lung parenchyma; clinical or diagnostic observations only | • Hold ICPI or proceed with close monitoring.  
• Monitor patients weekly with history and physical examination, pulse oximetry; may also offer chest imaging (CXR, CT) if uncertain diagnosis and/or to follow progress.  
• Repeat chest imaging in 3-4 weeks or sooner if patient becomes symptomatic.  
• In patients who have had baseline testing, may offer a repeat spirometry or DLCO in 3-4 weeks.  
• May resume ICPI with radiographic evidence of improvement or resolution if held. If no improvement, should treat as G2. |
| 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 clinical improvement to ≤G1.  
• Prednisone 1-2 mg/kg/d and taper over 4-6 weeks.  
• Consider bronchoscopy with BAL +/- transbronchial biopsy.  
• Consider empiric antibiotics if infection remains in the differential diagnosis after workup.  
• Monitor at least once per week with history and physical examination, pulse oximetry, consider radiological imaging; if no clinical improvement after 48-72 hours of prednisone, treat as grade 3.  
• Pulmonary and infectious disease consults if necessary. |
| G3: Severe symptoms; Hospitalization required: Involves all lung lobes or > 50% of lung parenchyma; limiting self-care ADL; oxygen indicated. | • Permanently discontinue ICPI.  
• Empirc antibiotics may be considered.  
• Methylprednisolone IV 1-2 mg/kg/d.  
• If no improvement after 48 hours, may add immunosuppressive agent. Options include infliximab or mycophenolate mofetil IV or IVIG or cyclophosphamide. Taper corticosteroids over 4-6 weeks.  
• Pulmonary and infectious disease consults if necessary.  
• May consider bronchoscopy with BAL ± transbronchial biopsy if patient can tolerate. |
| G4: Life-threatening respiratory compromise; urgent intervention indicated (intubation) | • Subset of patients may develop chronic pneumonitis and may require longer taper. Chronic pneumonitis is a described phenomenon where the incidence is not known, but < 2%. |

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### 4.0. Endocrine Toxicities

#### 4.1. Thyroid

#### 4.1.1. Primary Hypothyroidism

**Workup and Evaluation:**
- TSH, with the option of also including FT4, can be checked every 4-6 weeks as part of routine clinical monitoring for asymptomatic patients on ICPI therapy.
- TSH and FT4 should be used for case detection in symptomatic patients.
- Low TSH with a low FT4 is consistent with central hypothyroidism. Evaluate as per hypophysitis (see 4.3).
- Commonly develops after thyrotoxicosis phase of thyroiditis (4.1.2).

<table>
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<tr>
<th>Grading</th>
<th>Management</th>
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<tbody>
<tr>
<td><strong>G1:</strong> TSH &gt; 4.5 and &lt; 10 mIU/L and asymptomatic</td>
<td>- Should continue ICPI with monitoring of TSH (option for FT4) every 4-6 weeks as part of routine care.</td>
</tr>
</tbody>
</table>
| **G2:** Moderate symptoms, able to perform ADL. TSH persistently > 10 mIU/L | - May continue or hold ICPI until symptoms resolve to baseline.  
- Consider endocrine consultation for unusual clinical presentations, concern for central hypothyroidism, or difficulty titrating hormone therapy.  
- 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 goal of TSH within the reference range.  
- FT4 can be used to help interpret ongoing abnormal TSH levels on therapy, as TSH may take longer to normalize.  
- Once adequately treated, repeat testing every 6-12 months or as indicated for a change in symptoms. |
| **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 to assist with rapid hormone replacement.  
- Hospital admission for developing myxedema (bradycardia, hypothermia, altered mental status).  
- Inpatient endocrinology consultation can assist with IV levothyroxine dosing, steroids, and supportive care.  
- If there is uncertainty about whether primary or central hypothyroidism is present, hydrocortisone should be given before thyroid hormone is initiated.  
- Myxedema coma is a life-threatening emergency requiring admission and a high level of care.  
- Thyroid supplementation and reassessment as in G2. |

**Additional Considerations**
- For patients without risk factors (i.e., < 70 years old, not frail, and without cardiac disease or multiple comorbidities), full replacement can be estimated using ideal body weight for a dose of approximately 1.6 mcg/kg/d.
- For those over age 70 and/or frail patients with multiple comorbidities (including cardiac disease), consider titrating up from a lower starting dose of 25-50 µg.
- Elevated TSH can be seen in the recovery phase of thyroiditis. In asymptomatic patients with FT4 that remains in the reference range, it is an option to monitor before treating to determine whether there is recovery to normal within 3-4 weeks. Progression or development of symptoms should be treated as per G2.
- Development of a low TSH on therapy suggests over-treatment or recovery of thyroid function and dose should be reduced or discontinued with close follow up.
### 4.0. Endocrine Toxicities

#### 4.1.2. Thyrotoxicosis

**Workup and Evaluation:**
- TSH can be checked every 4-6 weeks as part of routine clinical monitoring for asymptomatic patients on ICPI therapy.
- TSH and FT4 should be used for case detection in symptomatic patients. T3 can be helpful in highly symptomatic patients with minimal FT4 elevations.
- Low TSH with a low FT4 is consistent with central hypothyroidism. Evaluate as per hypophysitis (see 4.3).
- Consider TSH receptor antibody testing if there are clinical features and suspicion of Graves’ disease (e.g., ophthalmopathy and T3 toxicosis).

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<tr>
<th>Grading</th>
<th>Management</th>
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| **G1: Asymptomatic or mild symptoms** | - Can continue ICPI.  
- Beta-blocker (e.g., atenolol or propranolol) for symptomatic relief.  
- Close monitoring of thyroid function every 2-3 weeks after diagnosis to catch the transition to hypothyroidism, the most common outcome for transient subacute thyroiditis.  
- Treat transition to elevated TSH and low FT4 as for primary hypothyroidism (see 4.1.1).  
- For persistent thyrotoxicosis (> 6 weeks) consider endocrine consultation for additional work up. |
| **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.  
- For persistent thyrotoxicosis (> 6 weeks) refer to endocrinology for additional workup and possible medical thyroid suppression. |
| **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 for all patients.  
- Beta-blocker (e.g., atenolol or propranolol).  
- Hydration and supportive care.  
- Consider hospitalizing patients in severe cases as in-patient endocrine consultation can guide the use of additional medical therapies including steroids, potassium iodide (SSKI), or thionamide (methimazole or propylthiouracil) and possible surgery. |

#### 4.2. Adrenal

##### 4.2.1. Primary Adrenal Insufficiency

**Workup and Evaluation:**
- Evaluate AM levels of ACTH (if > 2× ULN) and cortisol level (if < 3 µg/dL).
- Basic Metabolic Panel (Na, K, CO2, and glucose).
- Renin and aldosterone.
- Consider standard dose ACTH stimulation test for indeterminate results (AM cortisol > 3 µg/dL and < 15 µg/dL).
- Evaluate for precipitating cause of crisis such as infection.
- Adrenal CT for metastasis or hemorrhage (most common causes of primary AI).
### 4.0. Endocrine Toxicities

<table>
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<tr>
<th>Grading</th>
<th>Management</th>
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| **All Grades** | • Referral to endocrinology.  
• Education on steroid stress dosing, emergency injections, and a medical alert bracelet/necklace, accessory, or system. |
| **G1: Asymptomatic or mild symptoms** | • Consider holding ICPI until patient is stabilized on replacement hormone.  
• Endocrine consultation.  
• Initiate replacement therapy with hydrocortisone (15-20 mg in divided doses – see additional considerations).  
• Titrate hydrocortisone to maximum of 30 mg daily total dose for residual symptoms of AI.  
• Reduce maintenance dosing for symptoms of iatrogenic Cushing’s syndrome (e.g., bruising, thin skin, edema, weight gain, hypertension, and hyperglycemia).  
• Most primary AI will also require fludrocortisone (starting dose 0.5-0.1 mg/d). Adjust based on volume status, sodium level, and renin response (target upper half of the reference range). |
| **G2: Moderate symptoms, able to perform ADL** | • Consider holding ICPI until patient is stabilized on replacement hormone.  
• Endocrine consultation.  
• See in clinic to assess need for hydration, supportive care, and hospitalization.  
• Initiate outpatient corticosteroid treatment at 2-3 times maintenance (e.g. hydrocortisone 30-50 mg total dose or prednisone 20 mg daily) to manage acute symptoms.  
• Initiate fludrocortisone (0.5-0.1 mg/d).  
• Decrease stress dose corticosteroids down to maintenance doses after 2 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.  
• Inpatient management may be needed to provide:  
  o Normal saline (at least 2L).  
  o IV Stress dose steroids: Hydrocortisone 50-100 mg Q 6-8 hours initial dosing.  
• Taper stress dose corticosteroids down to oral maintenance doses over 5-7 days.  
• 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 hypophysitis in section 4.3 for secondary (central) adrenal insufficiency.  
- Using hydrocortisone allows for re-creation of the diurnal rhythm of cortisol. Typically, 2/3 of the dose is given in the morning and 1/3 in the early afternoon. Long-acting steroids such as prednisone, rather than short-acting hydrocortisone, carry risk of over replacement but can be used in special circumstances, for example, if a patient is not able to adhere to a short-acting steroid regimen. Hydrocortisone 20 mg is equivalent to prednisone 5 mg.  
- DHEA replacement is controversial but deficiency can be tested and replacement considered in women with low libido and/or energy who are judged to be otherwise well replaced.  
- All patients need education on stress dosing for sick days, use of emergency injectables, when to seek medical attention for impending adrenal crisis, and a medical alert bracelet/necklace for adrenal insufficiency to trigger stress dose corticosteroids by emergency medical personnel. Therefore, early endocrinology consultation is appropriate.  
- Endocrine consultation should be part of planning prior to surgery or high-stress treatments such as cytotoxic chemotherapy at any time during a patient’s care.
## 4.0. Endocrine Toxicities

### 4.3. Pituitary

#### 4.3.1. Hypophysitis

**Workup and Evaluation:**
- Evaluate ACTH (AM), cortisol (AM), TSH, free T4, and electrolytes.
- Consider standard dose ACTH stimulation testing for indeterminate results (AM cortisol > 3 µg/dL and < 15 µg/dL).
- Consider evaluating LH and testosterone in males, FSH, and estrogen in premenopausal females with fatigue, loss of libido and mood changes, or oligomenorrhea.
- Consider MRI brain w/wo contrast with pituitary/sellar cuts in all patients with new hormonal deficiencies and particularly those with multiple endocrine abnormalities ± new severe headaches or complaints of vision changes.
- Perform MRI brain w/wo contrast with pituitary/sellar cuts for all patients presenting with diabetes insipidus (DI is most commonly from metastatic disease).

<table>
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<tr>
<th>Grading</th>
<th>Management</th>
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</table>
| All Grades             | • Referral to endocrinology  
  • Education on steroid stress dosing, emergency injections, and a medical alert bracelet/necklace, accessory, or system.                                                                                     |
| **G1:** Asymptomatic or mild symptoms | • Consider holding ICPI until patient is stabilized on replacement hormones.  
  • Endocrine consultation.  
  • Corticosteroid replacement for adrenal insufficiency with preference for hydrocortisone (15-20 mg in divided doses – see additional considerations section 4.2).  
  • Initiate other hormone replacement only after any needed adrenal replacement to avoid precipitating adrenal crisis.  
  o Thyroid hormone replacement if needed using dosing as above for primary hypothyroidism, with a goal FT4 in the upper half of the reference range (TSH is not accurate in central hypothyroidism).  
  o Testosterone or estrogen therapy if needed in those without contraindications (e.g. prostate cancer, breast cancer, or history of DVT).  
  • Recommend education on stress dosing, emergency injectable, and a medical alert or necklace accessory or system. |
| **G2:** Moderate symptoms, able to perform ADL | • Consider holding ICPI until patient is stabilized on replacement hormones.  
  • Endocrine consultation.  
  • Clinic evaluation to assess need for steroids and volume repletion.  
  • Consider oral pulse dose therapy in patients with MRI findings of swelling or threatened optic chiasm compression (prednisone 1 mg/kg/d (or equivalent)). Taper over 1-2 weeks and transition to physiologic maintenance therapy once down to 5 mg prednisone equivalent.  
  • Hormonal suppletionation as in G1. |
### 4.0. Endocrine Toxicities

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<thead>
<tr>
<th>G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL</th>
</tr>
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</table>
| - Hold ICPI until patient is stabilized on replacement hormones.  
- Endocrine consultation.  
- Hospitalize or make an ED referral for:  
  o Normal saline (at least 2L) or monitored free water replacement if DI.  
  o IV Stress dose steroids: Hydrocortisone 50-100 mg Q6-8 hours initial dosing.  
  o Oral pulse dose therapy with Prednisone 1-2mg/kg daily (or equivalent) tapered over at least 1-2 weeks to physiologic maintenance in patients with significant swelling on MRI, optic chiasm compression, severe headache or visual changes.  
- Taper stress dose corticosteroids down to oral maintenance doses over 5-7 days.  
- Maintenance therapy as in G1. |

### Additional Considerations:
- Please be aware of the need to **start corticosteroids first** when planning hormone replacement therapy for multiple deficiencies as other hormones accelerate the clearance of cortisol and can precipitate adrenal crisis.  
- ACTH stimulation can give a false negative result early in hypophysitis as adrenal reserve declines slowly after pituitary stimulation is lost. In the presence of clinical uncertainty, opt for replacement and test for ongoing need at 3 months.  
- If Prednisone or equivalent is started for mild or moderate symptoms, consider lower doses (average daily dose over two months of less than 7.5 mg) due to report of reduced survival on higher doses.\(^{12}\)  
- All patients need education on stress dosing for sick days, use of emergency steroid injectables, when to seek medical attention for impending adrenal crisis, and a medical alert bracelet for adrenal insufficiency to trigger stress dose corticosteroids by EMS.  
- Steroid use for other irAEs can cause isolated central adrenal insufficiency with a low ACTH. In a patient with adrenal insufficiency, a recent history of treatment with corticosteroids, and no other central hormone deficiencies, the HPA axis should be tested for recovery after 3 months of maintenance therapy with hydrocortisone.  
- Laboratory confirmation of AI should not be attempted in patients given high dose corticosteroids for other irAEs until treatment is ready to be discontinued.  
- AM cortisol in a patient on corticosteroids is not diagnostic as the measurement of therapeutic steroids in the assay for cortisol varies. Hydrocortisone needs to be held for 24 hours and other steroids for longer before endogenous function is assessed. Consider consulting endocrinology for recovery and weaning protocols using hydrocortisone in patients with symptoms of AI after weaning off corticosteroids.

### 4.4. Diabetes

**Workup and Evaluation:**
- Monitor patients for symptoms of new or worsening DM (polyuria, polydipsia, fatigue).  
- Monitor glucose at baseline and with each treatment cycle while on therapy and at follow-up visits for at least 6 months.  
- Laboratory evaluation in suspected CIADM should include:  
  o Urine and/or serum ketones.  
  o Anion gap on a metabolic panel.  
  o Anti-GAD or anti-islet cell antibodies.  
  o C-peptide levels.
<table>
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<tr>
<th>Grading</th>
<th>Management</th>
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| **G1:** Asymptomatic or mild symptoms; T2DM with fasting glucose value > ULN to 160 mg/dL (> ULN to 8.9 mmol/L): No evidence of CIADM such as ketoacidosis or laboratory evidence of pancreatic autoimmunity. | - Can continue ICPi with close clinical follow-up and laboratory evaluation.  
- Refer to PCP for additional management or:  
  o May initiate oral therapy for those with new onset T2DM.  
  o Intensify medical therapy for those with worsening T2DM. |
| **G2:** Moderate symptoms, able to perform ADL; T2DM with fasting glucose value > 160 to 250 mg/dL (> 8.9 to 13.9 mmol/L). No ketoacidosis or metabolic derangements but other evidence of CIADM at any glucose level. | - May hold ICPi until glucose control is obtained.  
- Urgent endocrine consultation for any patient with new-onset CIADM.  
- Initiate insulin for CIADM (or as default therapy if there is any question about the diagnosis).  
- Referral to ED or hospital admission if unable to initiate therapy, urgent outpatient specialist evaluation is not available, developing ketoacidosis or other concern for CIADM. |
| **G3-4:** Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL; G3: > 250 - 500 mg/dL (> 13.9 - 27.8 mmol/L); G4: > 500 mg/dL (> 27.8 mmol/L). Ketoacidosis or other metabolic abnormality. | - Hold ICPi until glucose control is obtained with reduction of toxicity to ≤ G1.  
- Admit for inpatient management of DKA, volume and electrolyte resuscitation and insulin initiation.  
- Endocrine consultation for all patients.  
- Insulin therapy appropriate for all patients. |
### 4.0. Endocrine Toxicities

**Additional Considerations:**

- Insulin therapy should be used in any case with significant hyperglycemia pending additional diagnostic workup if mechanism of DM is not known.
- Long-acting insulin therapy alone is not sufficient for CIADM because of the absence of pancreatic function after beta-cell destruction.
  - Starting total daily requirement can be estimated at 0.3-0.4 units/kg/d.
  - Half of daily requirements are typically given in divided doses as prandial coverage while half should be administered as a once daily long-acting homolog. This requires self-monitoring 4 or more times daily or the use of a continuous glucose monitor.
  - Sliding scale insulin can be used in conjunction with multiple daily injection regimens to accommodate the variability in glucose levels.
  - Decreased requirements after the initial acute admission for DKA are commonly seen in the so-called honeymoon period.
  - Education is critical to learn skills like responding to hypoglycemia, anticipating exercise, monitoring for DKA, or carbohydrate counting and to transition to technologies such as insulin pumps. Early endocrinology consultation is a high priority for all patients.
- T2DM patients will need to increase the frequency of self-monitoring as therapy intensifies and agents that can cause hypoglycemia are added to their regimen.
- Steroids can exacerbate post-prandial hyperglycemia and endocrinology consult should be considered for initiating or managing insulin in patients with T2DM being started on high dose steroids. If insulin is used, the doses generally need to be adjusted again as steroids are tapered down.
5.0. Musculoskeletal Toxicities

5.1. Inflammatory Arthritis

**Workup and Evaluation:**

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, anti-CCP, and 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 arthrocentesis if septic arthritis or crystal-induced arthritis are suspected.
- Consider early referral to a rheumatologist, if there is joint swelling (synovitis) or if symptoms persist > 4 weeks.

G3-4:
- As for grade 2.
- Seek rheumatologist advice and review.
- Test for viral hepatitis B, C, and latent/active TB test prior to DMARD treatment. Repeated screening labs annually in patients who require biologic treatment for > 1 year until treatment is completed.

**Monitoring:**
- Patients with IA should be monitored with serial rheumatologic examinations, including inflammatory markers, every 4-6 weeks after treatment is instituted.

<table>
<thead>
<tr>
<th>Grading</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Grades</strong></td>
<td>Clinicians should follow reports of new joint pain to determine if IA is present. Question whether symptoms new since receiving ICPI.</td>
</tr>
<tr>
<td>G1: Mild pain with inflammation, erythema, or joint swelling</td>
<td>Continue ICPI. Initiate analgesia with acetaminophen and/or NSAIDs.</td>
</tr>
<tr>
<td>G2: Moderate pain associated with signs of inflammation, erythema, or joint swelling; limiting instrumental ADL</td>
<td>Consider holding ICPI. Escalate analgesia and consider higher doses of NSAIDs as needed. If inadequately controlled, initiate prednisone 10-20 mg/d or equivalent. If improvement, slow taper according to response during the next 4-6 weeks. If no improvement after initial 4 weeks, treat as G3. If unable to lower corticosteroid dose to below 10mg/d after 6-8 weeks, consider DMARD. Consider intra-articular steroid injections for large joints. Referral to rheumatology.</td>
</tr>
</tbody>
</table>
### 5.0. Musculoskeletal Toxicities

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>G3-4</td>
<td>Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self-care ADL</td>
</tr>
</tbody>
</table>

- 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 2 weeks or worsening in meantime, consider synthetic or biologic DMARD.
  - Synthetic: methotrexate, leflunomide, hydroxychloroquine, sulfasalazine alone or in combination.
  - Biologic: Consider anti-cytokine therapy such as TNFα or IL-6 antagonists. Note: As a caution, IL6 inhibition can cause intestinal perforation. While this is extremely rare, it should not be used in patients with concomitant immune-related colitis.
- 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.

### 5.2. Myositis

**Workup and Evaluation:**
- Complete rheumatologic and neurologic history regarding differential diagnosis and rheumatologic and neurologic 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; CK and aldolase. Transaminases (AST, ALT) and LDH can also be elevated.
- Troponin to evaluate myocardial involvement. Other cardiac testing such as ECG and echocardiogram or cardiac MRI (see CV section for further details).
- Autoantibody testing to evaluate possible concomitant myasthenia gravis (anti-AChR and anti-striational antibodies)
- 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 (e.g. anti-TIF1γ, anti-NXP2, and other myositis autoantibodies as indicated), especially if patient had muscle-related manifestations before receiving ICPI
- Urinalysis for rhabdomyolysis.

**Monitoring:**
- CK, ESR, CRP, aldolase if CK has not been elevated.

**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.
### 5.0. Musculoskeletal Toxicities

<table>
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<tr>
<th>Grading</th>
<th>Management of Myositis Alone&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
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</table>
| **G1:** Mild weakness with or without pain | • Continue ICPI.  
• If CK and/or aldolase are elevated and patient has muscle weakness may offer oral corticosteroids, starting prednisone at 0.5mg/kg/d. Offer analgesia with acetaminophen or NSAIDs for myalgia if there are no contraindications.  
• Consider holding statins. |
| **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 (×3 ULN or more), initiate prednisone or equivalent at 0.5-1 mg/kg/d.  
• May require permanent discontinuation of ICPI in cases with G2 symptoms if patient had other objective findings of severe muscle involvement such as very elevated enzymes, or extensive involvement as determined by EMG, MRI or histology). ICPI should not be restarted until CK is normal and clinical manifestations of myositis are resolved. |
| **G3-4:** Severe weakness with or without pain; limiting self-care ADL | • Hold ICPI.  
• Consider hospitalization for patients with severe weakness severely limiting mobility, respiratory, dysphagia, or rhabdomyolysis.  
• Urgent referral to rheumatologist and/or neurologist.  
• Initiate prednisone 1 mg/kg/d or equivalent.  
• For patients with severe compromise, start 1-2mg/kg of methylprednisolone IV or higher dose bolus.  
• Consider plasmapheresis in patients with acute/severe disease as guided by rheumatology/neurology.  
• Consider IVIG therapy, noting onset of action is slower. Note: Plasmapheresis immediately after IVIG will remove immunoglobulin.  
• Consider other immunosuppressant therapy including biologics (e.g. rituximab), TNFα or IL-6 antagonists if symptoms worsen or if no improvement after 2 weeks. Other synthetic immunosuppressants such as methotrexate, azathioprine, or mycophenolate mofetil could be considered for maintenance<sup>f</sup>, or if symptoms and CK levels do not resolve entirely after 4 weeks. Rituximab is used in primary myositis.<sup>14</sup>  
• Consider permanent discontinuation of ICPI. |

**Additional Considerations:**  
• Caution is advised with rechallenging.  
• With elevated transaminases, consider differential with immune-mediated hepatitis.
### 5.0. Musculoskeletal Toxicities

#### 5.3 Polymyalgia-like Syndrome

**Workup and Evaluation:**
- **G1**: Complete rheumatologic history regarding differential diagnosis and examination of all joints and skin. Rarely patients may also develop concomitant GCA. Check for symptoms of temporal arteritis, such as headache, visual disturbances, or jaw claudication. Urgent referral to ophthalmologist if present and consider temporal artery biopsy as permanent visual loss can occur within days of symptom onset.
- 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.

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<th>Grading</th>
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| **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, prednisone < 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 ≤ G2. However, note that cases of toxicity returning upon rechallenge have been reported.  
• Referral to rheumatology.  
• Should initiate prednisone 40 mg/d or equivalent. If no improvement or need for higher dosages for prolonged time, may offer a steroid sparing agent such as synthetic drugs (e.g. methotrexate) or biologic agents (e.g. IL-6 antagonists). Note: As caution, IL-6 inhibition can cause intestinal perforation. While this is extremely rare, it should not be used in patients with immune-related colitis.  
• Consider admission of patients with severe symptoms. |

**Additional Considerations:**
- IL-6 antagonists may be the preferred steroid-sparing agents for management of polymyalgia-like syndrome as they are already approved for use in patients with GCA.

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*E* Patients with myasthenia gravis-like syndrome or myocarditis and concomitant myositis should be hospitalized, please see neurologic or cardiovascular sections, respectively, for further information.

*F* Strongly urge maintenance with synthetic immunosuppressants be undertaken in collaboration with rheumatology or neurology.
6.0. Renal Toxicities

Nephritis and Renal Dysfunction – Diagnosis and Monitoring

Clinical Presentation\(^6,15\) and Diagnosis:

**Definite ICPI-related nephritis or AKI:**
Kidney biopsy-confirmed diagnosis compatible with ICPI nephritis or AKI, and after clinical review of risk factors.\(^H\)

**Probable ICPI-related nephritis or acute renal failure:**
BOTH of the following:
- Sustained increase in serum creatinine ≥50% on at least two consecutive values or need for RRT, after clinical review of risk factors\(^H\)
- Absence of an alternative plausible etiology

AND at least one of the following:
- Sterile pyuria (≥5 WBCs/hpf)
- Concomitant or recent extrarenal irAE-eosinophilia (≥ 500 cells per µL)

**Possible ICPI-related nephritis or acute renal failure:**
BOTH of the following:
- Increase in serum creatinine ≥50%
- Need for RRT nephritis or AKI is not readily attributable to alternative causes

**Monitoring:**
- Monitor patients for elevated serum creatinine prior to every dose.
- Routine urinalysis is not necessary, other than to rule out UTIs etc.
- For any suspected immune-mediated adverse reactions, exclude other causes (see below).
- For suspected renal irAE obtain urinalysis, consider referral to nephrology
- For patients receiving combination therapy with immune checkpoint inhibitors and other agents, assess the potential contribution of the non-iCPI treatment to the renal failure
- Assess for concomitant medications, prescribed and OTC, herbals, vitamins, nephrotoxic agents, or contrast media
- If no potential alternative cause of AKI is identified, then one can assume it is ICPI related and should forego biopsy
- Swift treatment of autoimmune component is important.

6.1. Nephritis or Acute Kidney Injury

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<tr>
<td>G1: Creatinine level increase of &gt; 0.3 mg/dL; creatinine 1.5 - 2.0× above baseline</td>
<td>• Consider temporarily holding ICPI and/or other potential contributing agents in combination regimens, pending consideration of potential alternative etiologies (recent IV contrast, medications, fluid status, UTI) and baseline renal function. A change that is still &lt;1.5 ULN could be meaningful.</td>
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### 6.0. Renal Toxicities

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| **G2: Creatinine 2 - 3× above baseline** | • Hold ICPI temporarily.  
• Consult nephrology.  
• Evaluate for other causes (recent IV contrast, medications, fluid status, etc.) If other etiologies are ruled out, administer 0.5 to 1 mg/kg/d prednisone equivalents.  
• If worsening or no improvement after 1 week increase to 1 to 2 mg/kg/d prednisone equivalents and permanently discontinue ICPI.  
• If improved to ≤G1, taper steroids over at least 4 weeks.  
• If no recurrence of CRI discuss resumption of ICPI with patient after taking into account the risks and benefits. Resumption of ICPI can be considered once steroids have been successfully tapered to ≤ 10 mg/d or discontinued. |
| **G3: Creatinine >3× baseline or >4.0 mg/dL; hospitalization indicated** | • Permanently discontinue ICPI if ICPI is directly implicated in renal toxicity.  
• Consult nephrology.  
• Evaluate for other causes (recent IV contrast, medications, fluid status, UTI, etc.).  
• Administer corticosteroids (initial dose of 1 to 2 mg/kg/d prednisone or equivalent). |
| **G4: Life-threatening consequences; dialysis indicated; creatinine 6× above baseline** | • Permanently discontinue ICPI if ICPI is directly implicated in renal toxicity.  
• Consult nephrology.  
• Evaluate for other causes (recent IV contrast, medications, fluid status, UTI, etc.).  
• Administer corticosteroids (initial dose of 1 to 2 mg/kg/d prednisone or equivalent). |

### 6.2. Nephritis or Acute Kidney Injury – Follow Up

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| **G1: Creatinine level increase of >0.3 mg/dL; creatinine 1.5 - 2.0× above baseline** | If improved to baseline  
• Resume routine creatinine monitoring |
| **G2: Creatinine 2 - 3× above baseline** | If improved to Grade 1:  
• Taper corticosteroids over at least 4 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: Creatinine >3× baseline or >4.0 mg/dL; hospitalization indicated** | 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. infliximab, azathioprine, cyclophosphamide (monthly), cyclosporine, mycophenolate). |
| **G4: Life-threatening consequences; dialysis indicated; creatinine 6× above baseline** | 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. infliximab, azathioprine, cyclophosphamide (monthly), cyclosporine, mycophenolate). |

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**Note:**
- Adapted from Gupta 2020.\(^1\)
- Risk factors include prior or concomitant nephrotoxic agent(s) use, prior or concomitant extrarenal irAEs.\(^2\)
### 7.0. Nervous System Toxicities

#### 7.1. Myasthenia Gravis

**Workup and Evaluation:**
- AChR and anti-striated muscle antibodies in blood. If AChR antibodies are negative, consider MuSK and LPR4 antibodies in blood—while presence of antibodies is confirmatory, the absence of antibodies does not rule out the syndrome.
- Pulmonary function assessment with NIF and VC.
- 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
- Troponin, EKG, and consider TTE and/or cardiac MRI to evaluate concomitant myocarditis (see CV section for further details)
- Electrodiagnostic studies, under neurologic consultation, including neuromuscular junction testing with repetitive stimulation and/or jitter studies, NCS to exclude neuropathy, and needle EMG to evaluate for concomitant myositis
- Inflammatory markers (ESR and CRP).
- Consider paraneoplastic workup
- Review and stop medications with known risk of worsening myasthenia: beta-blockers, IV magnesium, fluoroquinolones, aminoglycosides, and macrolide antibiotics.

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<tr>
<td><strong>All Grades</strong></td>
<td>All grades warrant workup and intervention given potential for progressive MG to lead to respiratory compromise. Inpatient admission may be appropriate at all grades.</td>
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<tr>
<td>No G1</td>
<td>NA</td>
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| **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 and steroid taper completed.\(^\text{16}\)  
• Neurology consultation.  
• Strongly consider in-patient care as patients can deteriorate quickly.  
• Pyridostigmine starting at 30 mg PO three times a day and gradually increase to maximum of 120mg PO four times a day as tolerated and based on symptoms and wean based on improvement. These procedures should be done in close collaboration with the neurologist.  
• Administer corticosteroids (prednisone 0.5 mg/kg’ orally daily). 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) | • Follow G2 recommendations as listed, with the following additions for G3-4:  
• Permanently discontinue ICPi.  
• Admit patient, may need ICU-level monitoring.  
• Continue steroids, taper should begin 3-4 weeks after initiation then wean based on symptom improvement.  
• Initiate IVIG 2G/kg IV over 5 days (0.4G/kg/d) or plasmapheresis × 5 days.  
• Consider adding rituximab if refractory to IVIG or plasmapheresis.  
• Frequent pulmonary function assessment.  
• Daily neurologic review. |
### 7.0. Nervous System Toxicities

#### 7.2. Guillain-Barre Syndrome

**Workup and Evaluation:**
- Neurologic consultation
- MRI spine w/wo contrast (rule out compressive lesion and evaluate for nerve root enhancement/thickening)
- Lumbar puncture: CSF analysis for cell count and differential, cytology for malignant cells, protein, glucose, and viral/bacterial cultures. Note that CSF typically has elevated protein and often elevated WBC as well even though this is not typically seen in classical Guillain-Barre.
- Consider paraneoplastic workup eg ANNA-1 antibody testing
- Serum antiganglioside antibody tests for GBS and its subtypes (eg, anti-GQ1b for Miller Fisher variant associated with ataxia and ophthalmoplegia).
- Flow cytometry in patients with hematological malignancies
- Electrodiagnostic studies (NCS and EMG) to evaluate polynuropathy
- Pulmonary function testing (NIF or VC)
- Frequent neuro checks

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<th>Grading</th>
<th>Management</th>
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<tbody>
<tr>
<td>No G1</td>
<td>NA</td>
</tr>
<tr>
<td>G2:</td>
<td>Moderate: some interference with ADLs, symptoms concerning to patient.</td>
</tr>
<tr>
<td>G3-4:</td>
<td>Severe: limiting self-care and aids warranted, weakness limiting walking, ANY dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms.</td>
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</table>
|           | • Discontinue ICPI.  
|           | • Neurology consultation  
|           | • Admission to inpatient unit with capability of rapid transfer to ICU-level monitoring.  
|           | • Start IVIG (0.4G/kg/d for 5 days for a total dose of 2G/kg) or plasmapheresis. Note: plasmapheresis immediately after IVIG will remove immunoglobulin.  
|           | • Corticosteroids are usually not recommended for idiopathic GBS, however in ICPI-related forms, a trial is reasonable (methylprednisolone 2-4 mg/kg/d), 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. After pulse steroids, taper steroids over 4-6 weeks.  
|           | • Frequent neuro checks and pulmonary function monitoring.  
|           | • Monitor for concurrent autonomic dysfunction.  
|           | • Non-opioid management of neuropathic pain, for example, pregabalin, gabapentin, or duloxetine.  
|           | • Treatment of constipation/ileus. |

**Additional Considerations:**
- Extreme caution with rechallenging for severe cases after complete resolution of symptoms and tapered off immunosuppression
### 7.0. Nervous System Toxicities

#### 7.3. Peripheral Neuropathy

**Workup and Evaluation:**

**G1:**
- Consider neurology consultation to guide neuropathy phenotype determination and workup
- Serum testing for reversible neuropathy causes: HbA1c, vitamin B12, TSH, vitamin B6, folate, serum protein electrophoresis, and immunofixation, CPK
- Consider additional testing guided by neuropathy phenotype: ANA, ESR, CRP, ANCA, anti-Smooth muscle, SSa/SSb, RNP, anti-dsDNA, ganglioside ab, anti-MAG, anti-Hu (ANNA-1 ab), thiamine, Lyme, hepatitis B or C, HIV
- Consider MRI spine w/wo contrast

**G2:** In addition to the above:
- MRI spine advised, MRI brain if cranial nerve involvement, MRI plexus if concern for plexus involvement
- Consider lumbar puncture: CSF analysis for cell count and differential, cytology for malignant cells, protein, glucose, and viral or bacterial cultures.
- Consider EMG/NCS

**G3-4:** go to GBS algorithm

<table>
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<tr>
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<tbody>
<tr>
<td>G1: Mild: no interference with function and symptoms not concerning to patient. Note: any cranial nerve problem should be managed as moderate</td>
<td>• Low threshold to hold ICPI and monitor symptoms for a week. If to continue, monitor very closely for any symptom progression.</td>
</tr>
</tbody>
</table>
| 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/d (if progressing from mild).  
• Gabapentin, 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.  
• Neurology consultation.  
• Initiate IV methylprednisolone 2-4 mg/kg/d and proceed as per GBS management |

### 7.4. Autonomic Neuropathy

**Workup and Evaluation:**

An evaluation by neurologist or relevant specialist depending on organ system, with testing which may include:
- Screen for other causes of autonomic dysfunction: diabetic screen, adrenal insufficiency, HIV, paraproteinemia, amyloidosis, botulism, consider chronic diseases such as Parkinson’s and other autoimmune screen.
- Orthostatic vital signs.
- Consider electrodiagnostic studies (NCS and EMG) to evaluate for concurrent polyneuropathy.
- Consider paraneoplastic autoimmune dysautonomia antibody testing (eg, anti-ganglionic AChR, ANNA-1, and N-type voltage-gated calcium channel antibodies).
### 7.0. Nervous System Toxicities

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<tbody>
<tr>
<td>G1: Mild: no interference with function and symptoms not concerning to patient.</td>
<td>• Low threshold to hold ICPi and monitor symptoms for a week. If to continue, monitor very closely for any symptom progression.</td>
</tr>
<tr>
<td>G2: Moderate: some interference with ADLs, symptoms concerning to patient.</td>
<td>• Hold ICPi and resume once return to ≤ G1 and off prednisone if used.</td>
</tr>
<tr>
<td></td>
<td>• Initial observation OR initiate prednisone 0.5-1mg/kg/d (if progressing from mild).</td>
</tr>
<tr>
<td>G3-4: Severe: limiting self-care and aids warranted.</td>
<td>• Permanently discontinue ICPi.</td>
</tr>
<tr>
<td></td>
<td>• Admit patient.</td>
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<tr>
<td></td>
<td>• Initiate methylprednisolone 1 g daily × 3 days followed by oral steroid taper.</td>
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<td></td>
<td>• Neurology consultation.</td>
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### 7.5. Aseptic Meningitis

**Workup and Evaluation:**
- MRI brain w/wo contrast with pituitary or sellar cuts protocol.
- AM cortisol, ACTH to rule out adrenal insufficiency.
- Strongly consider lumbar puncture with CSF analysis for opening pressure, cell count and differential, cytology for malignant cells that could indicate leptomeningeal metastases, protein, glucose, gram stain, viral/bacterial cultures, PCR for HSV, and other viral PCRs depending on suspicion.
- May see elevated WBC in CSF with normal glucose, normal culture, and gram stain. May see reactive lymphocytes, neutrophils, or histiocytes on cytology.

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<tr>
<td>G1: Mild: no interference with function and symptoms not concerning to patient.</td>
<td>• Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits.¹⁷</td>
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<tr>
<td></td>
<td>• Consider neurology consult</td>
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<td></td>
<td>• Consider empiric antiviral (IV acyclovir) and antibacterial therapy until CSF results.</td>
</tr>
<tr>
<td>G2: Moderate: some interference with ADLs, symptoms concerning to patient (i.e. pain but no weakness or gait limitation).</td>
<td>• Once bacterial and viral infection negative, may closely monitor off corticosteroids or consider oral prednisone 0.5-1 mg/kg/d or IV methylprednisolone 1 mg/kg/d if moderate or severe symptoms.</td>
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<td>• Steroids can be tapered after 2-4 weeks, monitoring for symptom recurrence.</td>
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<tr>
<td>G3-4: Severe: limiting self-care and aids warranted</td>
<td>• Consider hospitalization for G3-4.</td>
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7.0. Nervous System Toxicities

7.6. Encephalitis

**Workup and Evaluation:**
- 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 with CSF analysis for opening pressure, cell count and differential, cytology for malignant cells that could indicate leptomeningeal metastases, protein, glucose, gram stain, viral/bacterial cultures, PCR for HSV and other viral PCRs depending on suspicion, oligoclonal bands, autoimmune encephalopathy, and paraneoplastic panels.
- May see elevated WBC with lymphocytic predominance and/or elevated protein.
- EEG to evaluate for subclinical seizures.
- Serum studies: Chem panel, CBC, ESR, CRP, ANCA (if suspect vasculitic process), thyroid panel including TPO and thyroglobulin, am cortisol and ACTH, GQ1b antibodies (Bickerstaff encephalitis, rhomboencephalitis), celiac antibody panel, paraneoplastic and autoimmune encephalitis panels.
- Rule out concurrent anemia/thrombocytopenia, which can present with severe headaches and confusion.

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<th>Grading</th>
<th>Management</th>
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</table>
| 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/d.  
• Neurology consultation  
• If severe or progressing symptoms or oligoclonal bands present, consider pulse corticosteroids (methylprednisolone 1 g IV daily for 3-5 days) plus IVIG 2g/kg over 5 days (0.4 g/kg/d) or plasmapheresis.  
• Taper steroids following acute management over at least 4-6 weeks.  
• If positive for autoimmune encephalopathy or paraneoplastic antibody or limited or no improvement, consider Rituximab in consultation.  
• Admit patient for G3-4 |
| 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. Demyelinating Diseases, including multiple sclerosis, transverse myelitis, ADEM, ON and NMO

**Workup and Evaluation:**
- Neurologic consultation.
- Ophthalmic or neuro-ophthalmic evaluation if ocular involvement
- MRI with contrast of brain, orbit, cervical, and thoracic spinal cord (tailor to exam finding).
- Lumbar puncture with CSF analysis including autoimmune encephalitis panel and oligoclonal bands, CNS demyelinating disease antibodies (aquaporin 4 and myelin oligodendrocyte glycoprotein), viral PCRs especially JCV PCR to exclude progressive multifocal leukoencephalopathy.
- Serum studies: B12, HIV, RPR, ANA, Ro/La, TSH, aquaporin-4 IgG, paraneoplastic panel or anti-HU and anti-CRMP5-CV2, thyroid panel including TPO and thyroglobulin, am cortisol and ACTH, paraneoplastic and autoimmune encephalitis panels.
- Evaluation for urinary retention, constipation.
- EEG to evaluate for subclinical seizures.
- Although less common, biopsy may provide definitive evidence of CNS demyelination.
### 7.0. Nervous System Toxicities

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| **G1:** Asymptomatic or mild symptoms; clinical or diagnostic observations only | • Intervention not indicated.  
• Continue immunotherapy unless symptoms worsen or do not improve. |
| **G2:** Moderate symptoms; minimal, limiting age-appropriate instrumental ADL | • Stop ICPI.  
• Neurology consultation.  
• Start prednisone 1mg/kg daily and taper over 1 month.  
• Rule out infection. |
| **G3:** Severe or medically significant symptoms but not immediately life-threatening; limiting self-care ADL | • Permanently discontinue ICPI.  
• Neurology consultation.  
• Non opioid management of neuropathic pain, for example, pregabalin, gabapentin, or duloxetine.  
• Admit patient for methylprednisolone pulse dosing 1g/d and consider IVIG\(^J\) or plasmapheresis if no improvement or symptoms worsen after 3 days.\(^K\) |
| **G4:** Life-threatening consequences | • Permanently discontinue ICPI.  
• Neurology consultation.  
• ICU level inpatient care.  
• Start methylprednisolone pulse dosing 1g/d and consider IVIG or plasmapheresis if no improvement or symptoms worsen after 3 days.\(^K\) |

\(^1\) The divergence from 1mg/kg in the setting of MG is due to the potential short-term exacerbation of MG with high-dose steroid.  
\(^J\) IVIG 2g/kg, administered in divided doses per package insert.  
\(^K\) Plasmapheresis immediately after IVIG will remove immunoglobulin.
## 8.0. Hematologic Toxicities

### 8.1. Hemolytic Anemia

**Workup and Evaluation:**
- History and physical examination (with special consideration of history of new drugs, insect, spider, or snake bites)
- Blood chemistry, CBC with evidence of anemia, macrocytosis, evidence of hemolysis on peripheral smear. LDH, haptoglobin, bilirubin, reticulocyte count, free hemoglobin
- DIC panel which could include PT or INR or PTT, and infectious causes
- Autoimmune serology
- PNH screening
- Direct and indirect bilirubin, 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, parvovirus, iron, thyroid, infection
- Glucose-6-phosphate dehydrogenase level
- Evaluation of common drug causes (ribavirin, rifampin, dapsone, interferon, cephalosporins, penicillins, NSAIDS, Quinine/quinidine, fludarabine, ciprofloxacin, lorazepam, and diclofenac)
- Assessment of methemoglobinemia

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<tr>
<td>G1: Hgb &lt; LLN to 10.0 g/dL; &lt; LLN to 6.2 mmol/L; &lt; LLN to 100 g/L</td>
<td>- Continue ICPI with close clinical follow-up and laboratory evaluation.</td>
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</table>
| G2: Hgb < 10.0 to 8.0 g/dL; < 6.2 to 4.9 mmol/L; < 100 to 80g/L | - Hold ICPI and strongly consider permanent discontinuation.  
- Administer 0.5 to 1 mg/kg/d prednisone equivalents. |
| G3: Hgb < 8.0 g/dL; < 4.9 mmol/L; < 80 g/L; transfusion indicated | - Permanently discontinue ICPI.  
- Should use clinical judgment and consider admitting the patient.  
- Hematology consult.  
- Prednisone 1-2 mg/kg/d (oral or IV equivalent depending on symptoms/speed of development).  
- Consider RBC transfusion per existing guidelines. Do not transfuse more than the minimum number of 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, noncardiac inpatients).  
- Should offer patients supplementation with folic acid 1mg daily. |
| G4: Life-threatening consequences; urgent intervention indicated | - Permanently discontinue ICPI.  
- Admit patient.  
- Hematology consult.  
- IV prednisone corticosteroids 1-2 mg/kg/d.  
- If no improvement on or if worsening on corticosteroids or severe symptoms on presentation, initiate other immunosuppressive drugs, such as rituximab, IVIG, cyclosporine, infliximab, MMF, or ATG.  
- RBC transfusion per existing guidelines. Discuss with blood bank team prior to transfusions that a patient with possible ICPI SAE is in the hospital. |
### 8.0. Hematologic Toxicities

#### Additional Considerations:

Monitor hemoglobin levels weekly until the steroid tapering process is complete. Thereafter, less frequent testing is needed.\(^1\)

### 8.2. Acquired TTP

#### Workup and Evaluation:

- History with specific questions related to drug exposure (e.g. chemotherapy, sirolimus, tacrolimus, oxymorphone, antibiotics, and quinine)
- Hematology consult
- Physical exam, peripheral smear to check for schistocytes
- 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
- Consider CT or MRI brain, echocardiogram, electrocardiogram
- Cytomegalovirus serology
- Note: this disorder is usually associated with severe drop in platelets and hemolysis/anemia precipitously (microangiopathy)

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<tr>
<td>All Grades</td>
<td>• 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.</td>
</tr>
<tr>
<td>G1: Evidence of RBC destruction (schistocytosis) without anemia, renal insufficiency, or thrombocytopenia clinically</td>
<td>• 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. • Administer 0.5 to 1 mg/kg/d prednisone.</td>
</tr>
<tr>
<td>G2: Evidence of RBC destruction (schistocytosis) without clinical consequence with G2 anemia and thrombocytopenia</td>
<td>• 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.</td>
</tr>
<tr>
<td>G3: Laboratory findings with clinical consequences (G3 thrombocytopenia, anemia, renal insufficiency &gt; 2)</td>
<td>• In conjunction with hematology, initiate therapeutic PEX according to existing guidelines with further PEX dependent on clinical progress.(^1)(^2) • Administer methylprednisolone 1 g IV daily for 3 days, with the first dose typically administered immediately after the first PEX. For patient who has an initial platelet count response, discontinue PEX. • May offer rituximab • Consider caplacizumab if ADAMTS13 activity level is &lt; 10 IU/dL or &lt; 10% of normal, with an inhibitor or elevated anti-ADAMTS13 IgG.(^1)(^9) • If no exacerbation within 3-5 days after stopping PEX, taper steroids over 2-3 weeks, complete course of rituximab (if receiving) and discontinue caplacizumab (if receiving).(^2)</td>
</tr>
<tr>
<td>G4: Life-threatening consequences, (e.g., CNS hemorrhage or thrombosis/embolism or renal failure)</td>
<td>• 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. • In conjunction with hematology, initiate therapeutic PEX according to existing guidelines with further PEX dependent on clinical progress.(^1)(^2) • Administer methylprednisolone 1 g IV daily for 3 days, with the first dose typically administered immediately after the first PEX. For patient who has an initial platelet count response, discontinue PEX. • May offer rituximab • Consider caplacizumab if ADAMTS13 activity level is &lt; 10 IU/dL or &lt; 10% of normal, with an inhibitor or elevated anti-ADAMTS13 IgG.(^1)(^9) • If no exacerbation within 3-5 days after stopping PEX, taper steroids over 2-3 weeks, complete course of rituximab (if receiving) and discontinue caplacizumab (if receiving).(^2)</td>
</tr>
</tbody>
</table>
### 8.0. Hematologic Toxicities

#### 8.3. HUS

**Workup and Evaluation:**
- History and physical examination (special consideration for new history of high-risk drugs, hypertension, or cardiac causes)
- CBC with indices
- Blood smear morphology. Note that the presence of schistocytes on smear is critical for diagnosis
- Serum creatinine
- ADAMTS13 (to rule out TTP)
- Homocysteine or 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 diarrhea causes, shiga toxin, *Escherichia coli* 0157
- Direct antibody test (Coombs test), haptoglobin, LDH, and other etiologies of anemia
- Evaluation for common drugs causing hemolysis (tacrolimus, cyclosporine, sirolimus, etc.)
- Evaluation for neurologic changes (alteration in consciousness, concurrent confusion, seizures, pyramidal syndrome, and extrapyramidal syndrome with hypertonia)

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<th>Management</th>
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| **G1-2:** Evidence of RBC destruction (schistocytosis) without clinical consequences of anemia, thrombocytopenia grade 2 | • Continue ICPI with close clinical follow-up and laboratory evaluation.  
  • Supportive care |
| **G3:** Laboratory findings with clinical consequences (e.g., renal insufficiency and petechiae) | • Permanently discontinue ICPI.  
  • Hematology consult  
  • Begin therapy with eculizumab (anti-C5 antibody)  
  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 or embolism or renal failure) |
### 8.4. Aplastic Anemia

#### Workup and Evaluation:
- 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 and renal function
- Evaluation 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 and Management

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<tr>
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<th>Management</th>
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| **G1:** Mild: > 0.5 PMNs × 10⁹/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. |
| **G2:** Moderate: Hypocellular marrow < 25% and two of the following ANC < 500, peripheral platelet < 20,000 and reticulocyte < 2,000 | • Hold ICPI and provide growth factor support and close clinical laboratory evaluations daily.  
• Hematology consult  
• Administer horse ATG plus cyclosporine.  
• Supportive transfusions as per local guidelines. All blood products should be irradiated and filtered.  
• HLA typing and evaluation for bone marrow transplantation if patient is a candidate |
| **G3-4:** Severe: ANC < 200, platelet count < 20,000, reticulocyte count of < 20,000, plus hypocellular marrow < 25%. | • As per G2  
• Hold ICPI and monitor weekly for improvement. If not resolved, discontinue treatment until AE has reverted to G1.  
• If no response, repeat immunosuppression with rabbit ATG plus cyclosporine, cyclophosphamide.  
• For refractory patients consider eltrombopag plus supportive care. |

### 8.5. Lymphopenia

#### Workup and Evaluation:
- History (special attention to nutritional status and for lymphocyte depleting therapy such as fludarabine, ATG, steroids, cytotoxic chemotherapy, radiation exposure, etc. as well as history of autoimmune disease, family history of autoimmune disease)
- Physical exam with special attention to spleen size
- CBC with differential, peripheral smear, and reticulocyte count
- CXR for evaluation of presence of thymoma
- Bacterial cultures and evaluation for infection (fungal, bacterial, viral - specifically CMV or HIV)
### 8.0. Hematologic Toxicities

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| All Grades| - No specific action is required for lymphopenia G1-G3 and ICPI therapy should be continued.  
- For G4 (< 250 PB lymphocyte count), continue ICPI therapy and initiate *Mycobacterium avium* complex prophylaxis and *Pneumocystis jirovecii* prophylaxis, CMV screening. HIV and hepatitis screening if not already done.  
- May consider EBV testing if evidence of lymphadenopathy or hepatitis, fevers, hemolysis occur c/w lymphoproliferative disease occurs. |

### G1: Platelet count 75 to < 100/µL
- Continue ICPI with close clinical follow-up and laboratory evaluation.

### G2: Platelet count 50 to < 75/ µL
- Hold ICPI but monitor for improvement. If not resolved, interrupt treatment until AE has reverted to G1.  
- Administer prednisone 1 mg/kg per day (dosage range, 0.5–2 mg/kg per day) orally for 4 weeks followed by taper 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.

### G3: Platelet count 25 to < 50/ µL
- As per G2.  
- Hematology consult.  
- Consider as alternative to prednisone, dexamethasone 40mg daily for four days.  
- If IVIG is used, the dose should initially be 1 g/kg as a one-time dose.  
- 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* – consult for further details)

### G4: Platelet count < 25/µL
- As per G2.  
- Hematology consult.  
- Consider as alternative to prednisone, dexamethasone 40mg daily for four days.  
- If IVIG is used, the dose should initially be 1 g/kg as a one-time dose.  
- 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* – consult for further details)

### 8.6. ITP

**Workup and Evaluation:**
- History and physical examination (special attention for history of viral illness and lymphocyte depleting therapy such as fludarabine, ATG, steroids, cytotoxic therapy)  
- FH of autoimmunity or personal history of autoimmune disease  
- 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

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<tr>
<td>G1: Platelet count 75 to &lt; 100/µL</td>
<td>Continue ICPI with close clinical follow-up and laboratory evaluation.</td>
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</table>
| G2: Platelet count 50 to < 75/ µL | Hold ICPI but monitor for improvement. If not resolved, interrupt treatment until AE has reverted to G1.  
- Administer prednisone 1 mg/kg per day (dosage range, 0.5–2 mg/kg per day) orally for 4 weeks followed by taper 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. |
| G3: Platelet count 25 to < 50/ µL | As per G2.  
- Hematology consult.  
- Consider as alternative to prednisone, dexamethasone 40mg daily for four days.  
- If IVIG is used, the dose should initially be 1 g/kg as a one-time dose.  
- 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* – consult for further details) |
| G4: Platelet count < 25/µL | As per G2.  
- Hematology consult.  
- Consider as alternative to prednisone, dexamethasone 40mg daily for four days.  
- If IVIG is used, the dose should initially be 1 g/kg as a one-time dose.  
- 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* – consult for further details) |
### 8.0. Hematologic Toxicities

#### 8.7. Acquired Hemophilia A

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

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| **G1:** Mild: 5-40% of normal factor activity in blood; 0.05-0.4 IU/mL of whole blood | - Hold ICPI and discuss resumption with patient only after taking into account the risks and benefits.  
  - Administer 0.5 to 1 mg/kg/d prednisone.  
  - Transfusion support as required.  
  - 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.  
  - Administration of factor replacement (choice based on BU of titer).  
  - Administer 1 mg/kg/d prednisone ± rituximab (dose 375mg/m² weekly × 4 weeks) and/or cyclophosphamide (dose 1-2mg/kg/d). Choice of rituximab versus 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.  
  - Transfusion support as required for bleeding. |
| **G3-4:** Severe: < 1% of normal factor activity in blood; < 0.01 IU/mL of whole blood | - Permanently discontinue ICPI.  
  - Admit patient.  
  - 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 patients and those with CAD.  
  - Prednisone corticosteroids 1-2 mg/kg/d (oral or IV depending on symptoms) ± rituximab (dose 375mg/m² weekly × 4 weeks) and/or cyclophosphamide (dose 1-2mg/kg/d).  
  - Transfusion support as required for bleeding.  
  - If worsening or no improvement add cyclosporine or immunosuppression or immunoadsorption. |

**Additional Considerations:**
Acquired hemophilia A requires special 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.  

1. Patients should be immunized with a meningococcal vaccine at least 2 weeks prior to administering the first dose of eculizumab, unless the risks of delaying eculizumab therapy outweigh the risks of developing a meningococcal infection.
9.0. Cardiovascular Toxicities

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

Workup and Evaluation:
- ECG
- Troponin, and CPK to rule out concurrent myositis, especially in patients treated with combination immune therapies. Alternative reasons for elevation should be ruled out.
- If elevated, troponin should be serially monitored. With elevated troponin, be aware of the potential for triple M irAEs – myositis, myasthenia, and myocarditis – and refer to subspecialties.
- BNP
- Echocardiogram
- Chest X-ray

Additional testing to be guided by cardiology and may include:
- Stress test
- Cardiac catheterization
- Cardiac MRI

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| **G1:** Abnormal cardiac biomarker testing without symptoms and with no ECG abnormalities | • All grades warrant workup and intervention given the potential for cardiac compromise.  
• Hold ICPI for G1 elevated troponin and recheck troponin 6 hours later. May consider resuming once normalized or if believed not to be related to ICPI.  
• Hold ICPI and discontinue for ≥G2.  
• For patients with grade ≥2, early (i.e. within 24 hours) initiation of high-dose corticosteroids (1-2 mg/kg/d of prednisone, oral or IV depending on symptoms) should be considered as it is likely to be beneficial without adverse effects.  
• 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.  
• For new conduction delay, consider a pacemaker.  
• 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.\(^{26}\) Consider abatacept (costimulatory molecule blockade) or alemtuzumab (CD52 blockade) as additional immunosuppression in life threatening cases.\(^ {27,28}\) |

| **G2:** Abnormal cardiac biomarker testing with mild symptoms or new ECG abnormalities without conduction delay | **G3:** Abnormal cardiac biomarker testing with either moderate symptoms or new conduction delay |
| **G4:** Moderate to severe decompensation, IV medication or intervention required, life threatening conditions | **G4:** Moderate to severe decompensation, IV 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 (i.e. > 5mg/kg) in patients with moderate-severe heart failure.\(^ {29,30}\)
### 9.0. Cardiovascular Toxicities

### 9.2. Venous Thromboembolism

**Workup and Evaluation:**
Evaluation of signs and symptoms of PE or DVT may include:
- Clinical prediction rule to stratify patients with suspected VTE
- Venous ultrasound 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

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<th>Management</th>
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| **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, VKA, dabigatran, rivaroxaban, apixaban, or edoxaban for initial anticoagulation treatment. For long-term anticoagulation, LMWH, edoxaban, rivaroxaban, or apixaban for at least 6 months are preferred over VKAs because of improved efficacy.\(^{31,32}\)  
• IV heparin is an acceptable alternative for initial use and oral anticoagulants are acceptable for the long term. |
| **G3: Venous thrombosis (e.g., uncomplicated pulmonary embolism), urgent medical intervention indicated** | • Hold ICPI and may reintroduce after risk/benefit are considered.  
• Follow G2 anticoagulation recommendations. |
| **G4: Life-threatening consequences; hemodynamic or neurologic instability, organ damage; loss of extremity(ies)** | • Hold ICPI and may reintroduce after risk/benefit are considered.  
• Admit patient and management according to CHEST, ACC, and/or AHA guidelines and with guidance from cardiology.  
• Respiratory and hemodynamic support.  
• Follow G2 anticoagulation recommendations with further clinical management as indicated based on symptoms. |
### 9.0. Cardiovascular Toxicities

**Additional Considerations:**

- VTE prophylaxis in high-risk outpatients with cancer (Khorana score of 2 or higher prior to starting a new systemic regimen) may be offered thromboprophylaxis with apixaban, rivaroxaban, or LMWH provided there are no significant risk factors for bleeding and no drug interactions, as per ASCO VTE guideline.\(^{31}\)
- Although 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 judgment and take into account the risks and benefits when deciding whether to discontinue ICPI treatment.
- Anticoagulant therapy duration should continue while on immunotherapy and consideration be given to continuing for an additional 6 months following completion of immunotherapy.\(^{31}\)

\(^{M}\) According to CTCAE v5.0, G1 elevated troponin is defined as levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer.
10.0. Ocular Toxicities

**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
- Slight lamp exam
- Eye pressure
- Need to rule out myasthenia gravis

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

**Additional Considerations:**
Clinicians should be aware that ocular irAEs commonly accompany other organ irAEs, and there should be a high level of clinical suspicion, as symptoms may not always be associated with severity. Patients with all grades of ocular symptoms should be referred to ophthalmology.

### 10.1. Uveitis or Iritis

**Workup and Evaluation:** As per 10.0

Ophthalmology consult should be universal for the symptoms described in 10.0.

<table>
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| **G1:** Anterior uveitis with trace cells | - Continue ICPI.  
- Prompt referral to ophthalmology (usually within 1 week)  
- Artificial tears. |
| **G2:** Anterior uveitis with 1+ or 2+ cells | - Hold ICPI temporarily until after ophthalmology consult.  
- Urgent ophthalmology referral.  
- Topical corticosteroids (e.g. 1% prednisolone acetate suspension), cycloplegic agents (e.g. atropine), systemic corticosteroids.  
- May resume ICPI treatment once off systemic steroids if patient has only ocular irAE, once corticosteroids are reduced to ≤ 10mg prednisone equivalent. Continued topical/ocular steroids are permitted when resuming therapy to manage and minimize local toxicity.  
- Retreat after return to ≤ G1. |
| **G3:** Anterior uveitis with 3+ or greater cells; intermediate posterior or pan-uveitis | - Permanently discontinue ICPI.  
- Urgent ophthalmology referral.  
- Systemic corticosteroids and intravitreal or periocular or topical corticosteroids.  
- Methotrexate may be used in patients who respond poorly to systemic corticosteroids or those with severe sight-threatening inflammation. |
### 10.0. Ocular Toxicities

**G4: Best corrected visual acuity of 20/200 or worse in the affected eye**
- Permanently discontinue ICPI.
- Emergent ophthalmology referral.
- Systemic corticosteroids - prednisone 1-2mg/kg/d or methylprednisolone 0.8-1.6mg/kg/d and intravitreal or periocular or topical corticosteroids per ophthalmologist opinion.

**Additional Considerations:** Consider use of infliximab, other TNFα blockers, or IVIG in cases that are severe and refractory to standard treatment.\(^{34,35}\)

### 10.2. Episcleritis

**Workup and Evaluation:** As per 10.0

<table>
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<tr>
<th>Grading</th>
<th>Management</th>
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<tbody>
<tr>
<td><strong>G1: Asymptomatic</strong></td>
<td>Continue ICPI.</td>
</tr>
<tr>
<td></td>
<td>Prompt ophthalmology referral (usually within 1 week).</td>
</tr>
<tr>
<td></td>
<td>Artificial tears.</td>
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<tr>
<td><strong>G2: Vision 20/40 or better</strong></td>
<td>Hold ICPI therapy temporarily until after ophthalmology consult.</td>
</tr>
<tr>
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<td>Urgent ophthalmology referral.</td>
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<tr>
<td></td>
<td>Topical corticosteroids (e.g. 1% prednisolone acetate suspension), cycloplegic agents (e.g. atropine), systemic corticosteroids.(^{33})</td>
</tr>
<tr>
<td><strong>G3: Symptomatic and vision worse than 20/40</strong></td>
<td>Permanently discontinue ICPI.</td>
</tr>
<tr>
<td></td>
<td>Urgent ophthalmology referral.</td>
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<tr>
<td></td>
<td>Systemic corticosteroids and topical corticosteroids with cycloplegic agents.</td>
</tr>
<tr>
<td><strong>G4: 20/200 or worse</strong></td>
<td>Permanently discontinue ICPI.</td>
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<tr>
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<td>Emergent ophthalmology referral.</td>
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<td>Systemic corticosteroids and topical corticosteroids with cycloplegic agents.</td>
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**Additional Considerations:** Consider use of infliximab or other TNFα blockers in cases that are severe and refractory to standard treatment.\(^{34,35}\)
### 11.0. Systemic Toxicities

#### 11.1. Infusion-Related Reactions (IRRs)

**Workup and Evaluation:**
- Physical exam including vital signs
- Pulse oximetry
- ECG if chest pain or sustained tachycardia

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| **G1:** Mild transient reaction; infusion interruption not indicated; intervention not indicated | - Continue ICPI.  
- May consider premedication with acetaminophen and an antihistamine for subsequent infusions. |
| **G2:** Therapy or infusion interruption indicated but responds promptly to symptomatic treatment; prophylactic medication indicated for ≤ 24 hours | - Consider holding ICPI temporarily and/or reducing the rate of infusion to 50% (or per institutional guidelines).  
- Offer symptomatic treatment with antihistamines, NSAIDs, opioids, and IV fluids as clinically appropriate.  
- Offer prophylactic acetaminophen and an antihistamine per institution guidelines for subsequent infusions. |
| **G3:** Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae) | - Hold ICPI temporarily and consider resuming, at an infusion rate of 50% (or per institutional guidelines), once return to ≤ G1.  
- Offer symptomatic treatment with antihistamines, NSAIDs, opioids, and IV fluids as clinically appropriate.  
- Consider antihistamines and corticosteroid medications intravenously.  
- Hospitalization for other clinical sequelae. |
| **G4:** Life-threatening consequences; urgent intervention indicated | - Permanently discontinue ICPI.  
- ICU level inpatient care. |

**Additional Considerations:**
Clinicians may consider switching to an alternate agent in the therapeutic class upon rechallenge or consider rechallenging with the offending immunotherapy agent through a desensitization procedure under the supervision of an allergist.
12.0. Steroids

12.1. Pretreatment Considerations

- Baseline workup to include viral hepatitis B and C serology and consideration for latent or active TB test. In patients with pre-existing HIV, testing HIV viral load and CD4 count would be appropriate.
- Patients with preexisting comorbid conditions, such as DM, hypertension, HF, cataract, glaucoma, infection, or osteoporosis, should have their condition optimally managed prior to commencing steroids.
- Ideal steroid dosing and duration is individualized and can vary by patient, oncologic agents, and type of irAE. Please refer to each individual irAE section for more detail.
- The lowest dose of steroids should be used for the shortest duration of time needed to achieve treatment goals and control deleterious effects of irAE, as the risk of toxicity with steroids is generally dose- and duration-dependent.

12.2. Prevention of Opportunistic Infection

- Use of prophylaxis for an opportunistic infection with PJP may be considered once a patient has received a prednisone equivalent of ≥ 20 mg/d for 4 or more weeks or > 30 mg for 3 weeks or more. Physicians may proceed according to institutional guidelines.
- The role of prophylactic fluconazole with prolonged steroid use (> 12 weeks) remains unclear and physicians should proceed according to institutional guidelines.

12.3. Monitoring for Acute or Short-Term and Long-Term Adverse Effects

- Patients should be routinely asked about adverse effects related to glucocorticoids. During treatment with glucocorticoids and depending upon individual risk factors such as dose and duration of glucocorticoid usage, other medications being used, and comorbidities, particular attention should be given to the following acute/short-term and long-term adverse effects:
  
  **Acute/short-term AEs**
  - Increased vulnerability to infection
  - Insomnia
  - Anxiety
  - Diabetes or glucose intolerance
  - Hypertension
  - Cutaneous changes

  **Long-term AEs**
  - Bone loss (osteopenia and osteoporosis) and fractures
  - Cataracts or glaucoma
  - Steroid myopathy
  - Relative adrenal insufficiency
  - Psychiatric disturbance
  - Gastric or duodenal ulcers

- GI prophylaxis with PPI or H2 antagonist is recommended.
- To limit steroid-induced bone loss, patient should receive adequate calcium (dietary or supplementation), vitamin D, and weight-bearing exercise should be encouraged when feasible. Bone-modifying agents may be offered to patients on steroids for > 3 months and are recommended for all patients with pre-existing osteoporosis. Patients with or at risk for osteoporosis who have long-term survival potential should undergo bone mineral density testing.
12.0. Steroids

12.4. Tapering of Steroids

- The length of steroid-taper should occur according to the type and severity of irAE, the initial steroid dose, and individual patient responses rather than other prespecified criteria.
- Steroid taper should occur slowly, generally over 4-6 weeks.
- Regular clinical evaluation should occur during steroid tapering as there is a risk of irAE rebound or recurrence.
- In general, oral steroid tapering is recommended to occur over 4-6 weeks, with a reduction in prednisone or prednisolone of 10mg every 3-7 days (as irAE allows) until the dose is 10mg/d, then reduce by 5mg every 3-7 days for patients who respond quickly to steroids. For those who have received steroids for several weeks, tapering may be more prolonged.
- In general, for patients that require IV steroids, tapering is recommended to occur over 4 weeks or longer. The initial IV conversion from methylprednisolone if ≥ 1mg/kg/d would be to oral prednisone 1mg/kg/d at minimum and then taper as above.
- Longer steroid tapers (> 4-6 weeks) may be required for complete resolution or to avoid recurrence or rebound of irAE events.
- Patients should be monitored for the symptoms of adrenal insufficiency after prolonged exogenous steroids
- Stress doses may be needed in the event of injury, infection, and surgery
- Option when ready to drop below 5 mg of prednisone or 0.5 mg of dexamethasone after a longer course with concern for iatrogenic adrenal insufficiency, is to transition to hydrocortisone at physiologic dosing (10 mg in the morning, 5 mg in the afternoon). This allows for faster recovery of the HPA axis because it restores diurnal patterns.
- If indicated to control disease, a simultaneous slow, low dose taper of the long-acting steroid can be given (for example decreasing by 1 mg prednisone per week).
- HPA axis function can be tested 24 hours from last oral hydrocortisone (skip PM dose, hold AM dose for labs) - measured AM cortisol and ACTH will reflect endogenous function. Ambiguous results can be clarified with an ACTH stimulation test similarly prepared for.

Abbreviations.

ABG, arterial blood gas; ACC, American College of Cardiology; AChR, acetylcholine receptor; ACTH, adrenocorticotropic hormone; AD, autoimmune disease; ADEM, acute disseminated encephalomyelitis; ADL, activities of daily living; AE, adverse event; AGEP, acute generalized exanthematous pustulosis; AHA, American Heart Association; AI, adrenal insufficiency; aPTT, activated partial thromboplastin time; AKI, acute kidney injury; ALKP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, antinuclear antibody; ANC, antineutrophil cytoplasmic antibodies; ANCA, antineutrophil cytoplasmic antibodies; ANNA, antineuronal nuclear antibody; ASCO, American Society of Clinical Oncology; ASMA, anti-smooth muscle antibody; AST, aspartate aminotransferase; ATG, antithymocyte globulin; BAL, bronchoalveolar lavage; BM, bone marrow; BNP, brain natriuretic peptide; BSA, body surface area; BU, Bethesda unit; CAD, coronary artery disease; CBC, complete blood count; CCP, citrullinated protein antibody; CD4, cluster of differentiation 4; CHEST, American College of Chest Physicians; CIADM, checkpoint inhibitor-associated autoimmune diabetes; CK, creatine kinase; CMP, comprehensive metabolic panel; CMV, cytomegalovirus; CNS, central nervous system; COVID-19, coronavirus disease of 2019; CPK, creatine phosphokinase; CRI, chronic renal insufficiency; CRP, C-reactive protein; CSF, cerebrospinal fluid; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; CTLA-4, cytotoxic T-cell lymphocyte-4; CTPA, computed tomography pulmonary angiography; CV, cardiovascular; CXR, chest x-ray; DHEA, Dehydroepiandrosterone; DI, diabetes insipidus; DIC, disseminated intravascular coagulation; DIFF, differential test; DIHS, drug-induced hypersensitivity syndrome; DKA, diabetic ketoacidosis; DLCO, diffusing capacity of lung for carbon monoxide; DM, diabetes mellitus; DMD, disease-modifying antirheumatic drug; DRESS, drug reaction with eosinophilia and systemic symptoms; DVT, deep vein thrombosis; EBV, Epstein-Barr virus; EGG, electrocardiogram; ED, emergency department; EEG, electroencephalogram; EGD, esophagogastroduodenoscopy; EKG, electrocardiogram; ELISA, enzyme-linked immunosorbent assay; EMG, electromyography; EMS, emergency medical services; ESR, erythrocyte sedimentation rate; FEIBA, factor VIII inhibitor bypass activity; FH, family history; FSH, follicle-stimulating hormone; FLAIR, fluid attenuated inversion recovery; FT4, free thyroxine; G, grade; GAD, glutamic acid decarboxylase; GBS, Guillain-Barre Syndrome; GCA, giant cell arteritis; GD, Graves’ disease; GGT, gamma-glutamyl transpeptidase; GI, gastrointestinal; GPI, glycosylphosphatidylinositol; HBV, hepatitis B virus; HCV, hepatitis C virus; HF, heart failure; Hgb, hemoglobin; HHV6, human herpesvirus 6; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; HPA, hypothalamic pituitary adrenal; HSV, herpes simplex virus; HTN, hypertension; IA,
inflammatory arthritis; ICPI, immune checkpoint inhibitor therapy; ICU, intensive care unit; IgG, immunoglobulin G; JCV, John Cunningham virus; IL, interleukin; INR, international normalized ratio; irAE, immune-related adverse event; IRR, infusion-related reaction; ITP, immune thrombocytopenia; IV, intravenous; IVIG, intravenous immunoglobulin; JAK, Janus kinase; JCV, J virus; LDH, lactate dehydrogenase; LH, luteinizing hormone; LFT, liver function test; LLN, lower limit of normal; LMWH, low-molecular-weight-weight heparin; LPR4, lipoprotein related 4; MCV, mean corpuscular volume; MDS, myelodysplastic syndromes; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; MMA, methylmalonic acid; MMF, mycophenolate mofetil; MRI, magnetic resonance imaging; MuSK, muscle specific kinase; NA, not applicable; NASH, nonalcoholic steatohepatitis; NCS, nerve conduction study; NIF, negative inspiratory force; NMO, neuromyelitis optica; NSAID, nonsteroidal anti-inflammatory drug; O&P, ova and parasite test; ON, optic neuritis; OTC, over-the-counter; PB, peripheral blood; PCP, primary care practitioner; PCR, polymerase chain reaction; PD-1; programmed death 1; PD-L1, programmed death ligand 1; PE, pulmonary embolism; PEX, plasma exchange; PJP, pneumocystis jirovecii pneumonia; PMN, polymorphonuclear cell; PNH, paroxysmal nocturnal hemoglobinuria; PO, by mouth; PPI, proton pump inhibitor; PT, prothrombin time; PTT, partial thromboplastin time; Q, every; QID, four times a day; RBC, red blood cell; RF, rheumatoid factor; RNP, ribonucleoprotein; RPR, rapid plasma regain; RRT, renal replacement therapy; SAE, severe adverse event; SCAR, Severe Cutaneous Adverse Reaction; SJS, Stevens-Johnson syndrome; SSA, Sjögren’s syndrome A; SSB, Sjögren’s syndrome B; SSKI, potassium iodide; T2DM, type 2 diabetes mellitus; T3, triiodothyronine; TB, tuberculosis; TENS, toxic epidermal necrolysis; TID, three times a day; TNFα, tumor necrosis factor alpha; TPMT, thiopurine methyltransferase; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone; TTE, transthoracic echocardiogram; TTP, thrombotic thrombocytopenic purpura; UA, urinalysis; ULN, upper limit of normal; US, ultrasound; UTI, urinary tract infection; VC, vital capacity; VKA, vitamin K agonist; V/Q, ventilation/perfusion; VTE, venous thromboembolism; WBC, white blood cell.

References.

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