

# Follow-up and Management of Checkpoint Inhibitor Related Toxicities in Cancer Patients

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## Background

Immune checkpoint inhibitors (CPIs) are monoclonal antibodies (mAb) which increase antitumour activity by blocking intrinsic downregulators of immunity. The primary targets of CPIs include the programmed cell death-1 (PD-1) and its ligand PD-L1, as well as cytotoxic T lymphocyte-associated antigen 4 (CTLA-4). CPIs are effective in a broad range of cancers and it is anticipated that their indication will continue to expand to a number of additional malignancies.<sup>1</sup> Currently, their use is approved in the setting of melanoma, non-small cell lung carcinoma, renal cell carcinoma, and bladder cancer.<sup>1</sup> Additionally, CPI therapy has shown utility in other malignancies, including head and neck squamous cell, gastric, hepatocellular and ovarian cancers, certain types of breast or colorectal cancer, and Hodgkin lymphoma.<sup>1,2</sup>

Drugs in this class include ipilimumab, a selective humanized IgG-4 kappa monoclonal antibody that inhibits CTLA-4 to ultimately activate T cells against malignant tumour cells.<sup>3</sup> Ipilimumab was approved for use in Canada in 2012. The PD-1 targeting monoclonal antibodies nivolumab and pembrolizumab were approved in 2015.<sup>3</sup>

Immunotherapies are associated with better tolerance overall compared to traditional chemotherapy agents<sup>2</sup>. By modulating the activity of immune system, immune checkpoint blockade can cause inflammatory side effects, termed immune-related adverse events. Immune-related adverse events (irAEs) are toxicities caused by non-specific activation of the immune system and can affect almost any organ system. Most commonly these irAEs can be organized into the following categories: dermatologic, pulmonary, gastrointestinal, hepatic, and endocrine.<sup>1</sup> Other rarer and potentially life-threatening toxicities can also occur, involving the central nervous system, cardiovascular, musculoskeletal, and hematologic systems and treatment-related deaths have been reported in up to 2 percent of patients in clinical trials.<sup>1,4,5</sup> irAEs resulting from CPI therapy can have delayed onset and prolonged duration compared to chemotherapy, primarily due to pharmacodynamics differences.<sup>5</sup> For this reason, the clinician needs to remain vigilant. The management approach to irAEs is primarily based on clinical experience, as no prospective trials are available to inform irAE treatment strategies. There is a wide spectrum of potential immune-mediated toxicities which requires collaborative, multidisciplinary management.<sup>4</sup>

The underlying pathophysiology of irAEs is thought to be secondary to the role that immune checkpoints play in maintaining immunologic homeostasis.<sup>4</sup> The precise mechanisms that result in irAEs are still being elucidated but potential mechanisms include increasing T cell activity against antigens that are present in tumours and healthy tissue, increasing levels of pre-existing autoantibodies, increase in levels of inflammatory cytokines, and enhanced complement mediated inflammation.<sup>4</sup> PD-1 is thought to inhibit T cells at later stages of the immune response in peripheral tissues, whereas CTLA-4 is believed to act at a more proximal step in immune response, acting in several ways including attenuating T cell response. The irAEs are also different between these two classes of mAb, with more severe toxicities often seen in patients treated with CTLA-4 inhibitors.<sup>6</sup>

**Table 1.** Checkpoint Inhibitors Approved and Funded for Use in Alberta (as of February 2022)

Agent	Target	Approved Tumour sites
atezolizumab (Tecentriq)	PD-L1 mAb	Non-small cell lung cancer, hepatocellular carcinoma <i>Special access:</i> bladder cancer, triple negative PD-L1 positive breast cancer
ipilimumab (Yervoy)	CTLA-4 mAb	Melanoma
ipilimumab (Yervoy) + nivolumab (Opdivo)	PD-L1 mAb	Renal cell carcinoma <i>Special access:</i> mesothelioma, non-small cell lung cancer
nivolumab (Opdivo)	PD-1 mAb	Melanoma, renal cell carcinoma, non-small cell lung cancer, head and neck squamous cell carcinoma, Hodgkin lymphoma <i>Special access:</i> gastric adenocarcinoma, esophageal or GE junction cancer
pembrolizumab (Keytruda)	PD-1 mAb	Melanoma, non-small cell lung cancer, head and neck squamous cell carcinoma, urothelial carcinoma, gastric adenocarcinoma, Hodgkin lymphoma, renal cell carcinoma <i>Special access:</i> MMR deficient tumours, bladder cancer, esophageal cancer, triple negative breast cancer, MSI-H endometrial cancer
avelumab (Bavencio)	PD-L1 mAb	Merkel cell carcinoma, urothelial carcinoma
durvalumab (Imfinzi)	PD-L1 mAb	<i>Special access:</i> non-small cell lung cancer, bladder cancer
cemiplimab (Libtayo)	PD-1 mAb	Cutaneous squamous cell carcinoma <i>Special access:</i> basal cell carcinoma, non-small cell lung cancer

## Guideline Questions

1. What are the appropriate protocols for follow-up to monitor for irAEs in adult patients treated with checkpoint inhibitors for cancer?
2. What are the recommended management strategies for irAEs associated with checkpoint inhibitors in adult cancer patients?
3. Is it safe to restart treatment after an irAE?

## Search Strategy

PubMed was searched for articles published before March 2018 with the search terms 'immune checkpoint inhibitor', and 'adverse events', and 'cancer'. Additionally, guidelines from other organizations were included in the literature search. For a detailed description of the literature search and results, please see Appendix A.

## Target Population

The recommendations contained in this guideline are intended for use in adult patients over the age of 18 years who are being considered for or are receiving checkpoint inhibitors as part of their treatment for cancer. Different principles may apply to pediatric and adolescent patients.

## Recommendations

### General Approaches to Toxicity Management

1. It is widely acknowledged that cancer patients with pre-existing autoimmune disorders are at an increased risk of developing immune-related adverse events (irAEs). The treating oncologist should weigh the potential benefits of therapy against the risks of adverse events before deciding to proceed with treatment.
2. The current approach to managing irAES incorporates prevention, anticipation, detection, treatment and monitoring.<sup>1</sup> Patients on checkpoint inhibitors (CPI) should be monitored by a health care professional with experience identifying and managing irAEs.<sup>3</sup> Collaborative, multidisciplinary management should be employed by providers across a clinical spectrum. Patients may play an active role in detecting irAEs, therefore, education in early detection and reporting is paramount in the effective management of irAEs.
3. No prospective trials have defined the best strategies to manage irAEs. Recommendations for management are based upon expert opinion.
4. Immunosuppression is the mainstay of management of immune-mediate toxicity to reduce the state of inflammation. Glucocorticoids are the first-line agent used. If these are not sufficient to manage symptoms, additional immune modulatory drugs may be necessary (e.g. tumour necrosis factor antagonists, mycophenolate mofetil, anti-thymocyte globulin (ATG), calcineurin inhibitors, methotrexate, or intravenous immunoglobulin and plasmapheresis). These agents should be prescribed judiciously to reduce the risk of short-term and long-term toxicities.<sup>5</sup> Retrospective studies suggest that steroid use doesn't change effectiveness of CPI inhibitor therapy but other immunosuppressive medications have not been sufficiently studied.<sup>7,8</sup>

### Dermatology: Prevention Recommendations

1. At this time, it is not possible to accurately predict which patients are going to be more susceptible to immune-related dermatologic adverse events (irDAEs).
2. There is no role for pre-treatment with anti-inflammatory dose glucocorticoids to prevent irDAEs with CPI therapies. However, a low threshold for the initiation of irDAE empiric treatment must be maintained. Patients with pre-existing immune-related skin conditions such as psoriasis, bullous pemphigoid, or lupus should be closely monitored both by the treating medical oncologist and dermatologist.
3. Avoid skin irritants and excessive sun exposure to limit other aggravating factors to the skin.

## **Dermatology: Anticipation Recommendations**

1. Be aware of the potential immune-related dermatologic toxicities that may occur in patients on CPI therapy, and especially in those who have pre-existing immune-related skin conditions such as psoriasis, bullous pemphigoid, or lupus.
2. Patients should be counseled on the potential toxicities that may occur on therapy with these agents as well as the significance of potential symptoms that indicate these irAEs. Skin toxicities are among the most frequent AEs observed in patients treated with CPIs inhibiting either CTLA-4 (~45% with ipilimumab) or PD-1/PD-L1 (~35% with nivolumab and pembrolizumab) for all grade, but equal for grade 3 or higher (1-3%).<sup>9,10</sup> These are typically low grade in severity, and commonly present as maculopapular rash and pruritus. Vitiligo is commonly seen and reported exclusively in the melanoma population and is associated with response to therapy.<sup>11,12</sup> Less commonly, patients can develop lichenoid, eczematous, and bullous dermatitis, and psoriasis. Rare, life-threatening exfoliative conditions have been reported in the literature including Stevens-Johnson Syndrome/toxic epidermal necrolysis (SJS/TEN) and drug rash with eosinophilia and systemic symptoms (DRESS). Both patients and clinicians should be aware of the signs and symptoms of these life-threatening immune-mediated dermatologic toxicities.
3. Remain vigilant in monitoring for cutaneous toxicities. Skin toxicity typically occurs early on after initiation of therapy but there can be substantial variability in clinical presentation and timing of symptom onset. This mandates careful vigilance for signs of cutaneous toxicity at all points on therapy. Aside from causing potential morbidity and mortality, these are also well recognized factors in treatment patient non-compliance and discontinuation.

## **Dermatology: Detection Recommendations**

1. Complete a thorough physical examination of the skin including the mucosal membranes and an assessment including vital signs and lymph node assessment.
2. Rule out other potential etiologies including infection, other drug reaction, underlying systemic disease. Consider the possibility of a medical emergency including DRESS, acute febrile neutrophilic dermatosis (Sweet syndrome), SJS/TEN.
3. Complete biologic work-up including CBDd, liver enzymes/function, and renal function if indicated, complete directed serological studies if an autoimmune condition is suspected (e.g. screening antinuclear antibody (ANA) test, SS-A/Anti-Ro and SS-B/Anti-La if the rash exhibits photodistribution or photosensitivity, anti-histone, dsDNA) and can expand if clinically indicated. If patient is febrile, also complete blood cultures.

4. Recommend multidisciplinary assessment with dermatology consultation. May require punch biopsy and clinical photography.

**Table 2.** National Cancer Institute’s Common Terminology for Adverse Events (CTCAE) Classification for Cutaneous Toxicities

	Grade 1	Grade 2	Grade 3	Grade 4
Rash	Mild symptoms with no effect on QOL; avoid irritants, symptomatic management; can continue CPI	Symptoms affected QOL or diagnosis requiring intervention; symptomatic management, topical corticosteroids; can continue CPI with weekly clinical assessments	QOL and not responsive to standard therapy; hold CPI; systemic corticosteroids; urgent dermatology consult	Significantly affecting QOL and not responsive to standard interventions; hold CPI; systemic corticosteroids; urgent dermatology consult
SJS/TEN, DRESS	N/A	Maculopapular rash affecting 10-30% BSA with systemic symptoms, lymphadenopathy, or facial swelling; discontinue CPI, urgent dermatology consult	Skin erythema and sloughing <10% of BSA with evidence of mucosal involvement; discontinue CPI, urgent dermatology consult; admit to a burn unit and consult wound services	Skin erythema and sloughing ≥10% of BSA with evidence of mucosal involvement; discontinue CPI, urgent dermatology consult

### Dermatology: Treatment and Monitoring Recommendations

1. With the need for ongoing CPI therapy, treatment of dermatologic complications should occur with the involvement of a dermatologist experienced in the management of these complications.
2. Counsel patients to avoid skin irritants and sun exposure.
3. Supportive therapy for rash includes topical emollients, oral antihistamines as needed for pruritus, and topical corticosteroids:
  - **Grade 1 skin toxicity:** Patients should be treated with supportive therapy including topical emollients, oral antihistamines as needed for pruritus, and/or mild to moderate strength topical corticosteroids (hydrocortisone 2.5% or equivalent to triamcinolone 0.1% or equivalent). Counsel patients to avoid skin irritants and sun exposure. CPI therapy can be continued.
  - **Grade 2 skin toxicity:** Symptoms should be managed with topical emollients, oral antihistamines. Consider initiating prednisone (or equivalent) at 1mg/kg, tapering over at least 4 weeks. Treatment with CPIs can be continued but requires weekly assessment for clinical improvement. In the absence of improvement, therapy may need to be held until skin AE has reverted to grade 1.
  - **Grade 3 skin toxicity:** Treatment with CPI should be interrupted and consult with dermatology to determine the appropriateness of resuming when resolved to grade 1. Symptoms may be managed with topical emollients, oral antihistamines, and at least high strength topical corticosteroids. Systemic steroids should be initiated (prednisone 0.5-1mg/kg/day or equivalent dose of methylprednisolone), until rash improves to ≤ grade 1, tapering over at least 4 weeks.

- **Grade 4 skin toxicity:** Hold treatment with CPI and urgent dermatology consultation. Treat with high dose corticosteroids 1-2mg/kg with slow tapering when toxicity resolves. Patient may need admission to hospital. Monitor closely for progression to severe cutaneous adverse reaction. It is still unclear whether therapy can be resumed in this patient population. Consideration of alternative systemic antineoplastic therapy may be appropriate over resuming ICPs if the skin irAE does not resolve to grade 1 or less. But, if CPIs are the patient's only option, consider restarting once these adverse effects have resolved to grade 1.
4. In cases of suspected SJS or any mucous membrane involvement, discontinue CPI treatment and monitor for improvement, regardless of grade. Urgent dermatology consultation. Initiate therapy with topical emollients, oral antihistamines, and medium- to high strength topical corticosteroids depending on the severity. *Note: the usual prohibition of corticosteroids for SJS is not relevant here, as the underlying mechanism for the irAE is T-cell immune-directed toxicity.*
  5. In the setting of grade 3 or high cases of SJS, admit to a burn unit and consult wound services with attention to supportive care, including maintenance of fluid and electrolyte balance, minimizing insensible water losses, and preventing infection. If there is evidence of mucous membrane involvement, consulting other services to guide management in preventing sequelae from scarring (e.g. ophthalmology; ear, nose, and throat; urology; gynecology; etc, as appropriate). IVIG or cyclosporine may be considered in severe or steroid-unresponsive cases. **Do not re-challenge with CPI in the future.**
  6. Continue to monitor closely for resolution of these symptoms, especially if patients are maintained on CPI therapy. It is unclear what the effect CPI therapy has on the underlying malignancy in patients who develop significant immune-related cutaneous AEs. For example, studies suggest that the development of rash and vitiligo may correlate to response to CPI in patients being treated for melanoma, suggesting that some toxicities may actually be a surrogate for treatment response.<sup>11,13</sup>
  7. Where prolonged corticosteroid treatments are used, consider PJP prophylactic antibiotics, proton pump inhibitors, calcium, and Vitamin D.

### **Pulmonary: Prevention Recommendations**

1. Careful patient selection is recommended. At this time, it is not possible to accurately predict which patients are going to be more susceptible to immune-related pulmonary adverse events (irPAEs). There is no role for baseline serology, imaging, or other testing. Take caution in patients with underlying lung disease thought to be from an immune-mediated cause.



## **Pulmonary: Anticipation Recommendations**

1. Be aware of the potential immune-related pulmonary toxicities that may occur in patients on CPI therapy. Pulmonary irAEs can be challenging to diagnose as they typically have non-specific presentations (e.g. cough, dyspnea).
2. Patients should be counseled on the potential toxicities that may occur on therapy with these agents as well as the significance of potential symptoms that indicate these irAEs. Pneumonitis is the most common lung toxicity observed and accounts for one of the highest rates of CPI-related mortality.<sup>5</sup> The incidence of pneumonitis is higher in patients treated with PD-1/PD-L1 therapy than with CTLA-4 therapy. The combination of PD-1/PD-L1 therapy and anti-CTLA-4 mAbs significantly increases the risk of pneumonitis.<sup>5</sup> Rates of any grade pneumonitis have been documented in 2-5% of patients of patients treated with PD-1 therapy, with 1-2% grade  $\geq 3$  events. In patients treated with combination PD-1/CTLA-4 therapy this increases to 5-10% for any grade toxicity, and up to 4% grade  $\geq 3$  events<sup>14,15</sup>.
3. Have a low threshold for further investigation in patients being treated with CPIs. Pneumonitis secondary to CPIs can have a wide range of variability both in timing of onset and presentation from a clinical and radiographical perspective<sup>16</sup>.

## **Pulmonary: Detection Recommendations**

1. Pulmonary irAEs can be very challenging to identify due to their non-specific presentation and their occurrence in patients with either primary or metastatic malignancy in the lungs. Any new respiratory symptom should prompt a dedicated evaluation to rule out CPI-induced lung toxicity.
2. Complete a comprehensive history and physical exam considering infections processes, other potential drug reactions, radiotherapy, granulomatous diseases, and possible associations with interstitial lung disease.
3. Investigate including chest x-ray (repeat weekly if grade 2 or higher) and baseline bloodwork. Consider screening for viral, opportunistic, or bacterial infections, and consider pulmonary function tests as clinically indicated. A CT scan should be obtained if pneumonitis is suspected. Radiographic features of pneumonitis are not pathognomonic and can have variable appearance including ground glass opacifications, reticular pattern, and focal areas of consolidation. These may reflect patterns consistent with organizing pneumonia or hypersensitivity pneumonitis.<sup>17</sup>
4. Typically a lung biopsy is not required for diagnosis. However, if there is clinical or radiographical doubt about the etiology of the presentation then bronchoscopy with bronchoalveolar lavage and biopsy may be helpful. This may rule out acute infection, lepidic or lymphatic spread of disease or other pulmonary inflammatory changes.

**Table 3.** National Cancer Institute’s CTCAE Classification for Pneumonitis (Version 4)

Grade 1	Grade 2	Grade 3	Grade 4
Asymptomatic, radiographic changes only; clinical or diagnostic observations only; hold CPI	Mild to moderate symptoms, limiting IADLs, oxygen not indicated; start steroids immediately, hold CPI	Severe symptoms limiting BADLs, oxygen indicated; admit to hospital; permanently discontinue CPI	Life-threatening respiratory compromise, urgent intervention required, ARDS; admit to hospital; permanently discontinue CPI

### **Pulmonary: Treatment and Monitoring Recommendations**

1. Pneumonitis can have potentially life-threatening complications and therefore immunosuppressive medications should be started immediately in the setting of grade 2 or higher. If there is a suspicion of underlying infection, or in the case of a high-grade pneumonitis, patients may require bronchoscopy to rule out infection before starting immunosuppression. If the infectious status cannot be definitively determined, patients may require oral or IV antibiotics, particularly in the case of high-grade pneumonitis.
2. Grade 1 pneumonitis can be followed clinically and repeat radiographic imaging completed in 3-4 weeks. If there is evidence of radiographic improvement or resolution, can consider resuming CPI with close monitoring. If there is no improvement, should be treated as grade 2.
3. Grade 2 pneumonitis should be treated with oral corticosteroids at a dose of 1-2 mg/kg/day prednisone (or equivalent). Patients should receive close follow-up to ensure clinical improvement, with repeat chest x-ray in one week. Steroids should be slowly tapered over 4-6 weeks. If there is no clinical improvement after 48-72 hours, treat as grade 3. If there is resolution of symptoms and radiographic improvement to grade 1 or less, can consider re-challenging with CPI.
4. If pneumonitis is grade 3 or 4 the patient should be admitted to hospital. Treatment should consist of high-dose IV steroids, methylprednisolone 1-2 mg/mg/d. If there is clinical improvement, start slow taper over 6-8 weeks. If symptoms do not improve after 48-72 hours, additional immunosuppressive strategies should be employed. There is no standard agent in this setting, tumour necrosis alpha (TNF $\alpha$ ) inhibitors (e.g. infliximab 5 mg/kg IV), mycophenolate mofetil (MMF) (e.g. 1 g PO/IV bid), tocilizumab, and cyclophosphamide can all be considered. CPI therapy should be permanently discontinued.
5. Where prolonged corticosteroid treatments are used, consider PJP prophylactic antibiotics, proton pump inhibitors, calcium, and Vitamin D.

### **Gastrointestinal: Prevention Recommendations**

1. Recommend careful patient selection. Exhibit caution when considering therapy in a patient with underlying diagnosis of inflammatory bowel disease including Crohn’s disease or ulcerative colitis,

especially in those with severe underlying disease. These patients may be at higher risk for transient exacerbation of their underlying condition.<sup>4</sup>

2. There are currently no known agents to effectively prevent immune-mediate colitis. Studies with budesonide were found to be negative.<sup>18,19</sup>

### **Gastrointestinal: Anticipation Recommendations**

1. Be aware of the potential immune-related gastrointestinal (GI) toxicities that may occur in patients on CPI therapy. Have a high degree of clinical suspicion, as some of these toxicities can be non-specific.
2. Patients should be counseled on the potential toxicities that may occur on therapy with these agents as well as the significance of early detection and assessment. The most common presenting symptom is watery diarrhea. Other presenting symptoms include abdominal pain, weight loss, fever, and vomiting. Patients can also present with aphthous ulcers, fissures, and extra-intestinal manifestations of inflammatory bowel disease including skin changes and arthralgias. Upper GI symptoms including dysphagia and epigastric pain have also been reported.<sup>5</sup>
3. Have a low threshold for further investigation of GI toxicities in patients being treated with CPIs. Although these can occur with all agents, they are most commonly seen in patients treated with CTLA-4 inhibitors. GI toxicity is one of the most frequent and severe if the irAEs seen with anti-CTLA-4 therapy, with approximately one-third of treated patients developing irAEs related to the GI tract. These include aphthous ulcers, esophagitis, gastritis, diarrhea, and colitis. Diarrhea is the most common of these toxicities, occurring in 27-31% of patients with acute and chronic colitis seen in 8-22%. The rates of diarrhea and colitis are even higher in patients treated with a combination of anti-PD-1/PD-L1 and anti-CTLA4 agents.
4. The onset of immune-mediated GI toxicity typically occurs days to weeks after the start of therapy but can occur at any time even after discontinuation of the drug. Studies have shown the time course for colitis to be anywhere from 1-10 doses of ipilimumab with variable pattern.<sup>20-22</sup> It is seen less commonly with PD-L1 therapy with a median onset of 3 months.
5. At this time, it is not possible to predict which patients are going to be more susceptible to colitis from CPI therapy. Ongoing studies are evaluating the role of microbiome composition of a patient's gastrointestinal flora in the development of immune-mediated colitis as well as genetic factors.<sup>23</sup>

## Gastrointestinal: Detection Recommendations

1. Gastrointestinal irAEs are common and can be potentially severe, therefore both patients and clinicians should recognize the importance of early detection and investigation.
2. Complete a comprehensive history and physical exam in patients with diarrhea while on CPI therapy considering infections processes, exposures, and other drugs (including antibiotics).
3. Bloodwork should be completed to evaluate for complications including CBC, electrolytes, serum albumin, urea, creatinine. Inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) can be helpful.
4. Rule out infectious causes of diarrhea including viral (CMV in particular) and bacterial pathogens. Complete stool tests for enteric pathogens including *Clostridium difficile* toxin. Be aware that immune mediated colitis and infectious colitis can co-occur.
5. Investigate using abdominal x-ray and CT as clinically indicated. These investigations are useful to rule out obstruction, perforation and toxic megacolon.
6. Patients who develop persistent or high-grade ( $\geq$ grade 2) symptoms should be assessed with endoscopy. Immune-mediated colitis typically affects the rectum and sigmoid colon, so sigmoidoscopy is typically sufficient for diagnosis. It may appear as areas of erythema, erosions, exudates, and ulceration. Be aware that normal appearance of endoscopy does not rule out colitis, and biopsies must be obtained.<sup>24</sup> There is evidence that the presence of ulceration may be predictive of a steroid-refractory course, and these patients may require early infliximab.<sup>25,26</sup>
7. Screening laboratory investigations such as HIV, hepatitis as well as TB testing should be done in patients who may require infliximab.

**Table 4.** National Cancer Institute’s CTCAE Classification for Diarrhea and Colitis (Version 4).

	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	Increase in <4 stools per day over baseline, mild increase in ostomy output over baseline; can continue CPI with close monitoring; monitor hydration status; supportive care with anti-diarrheals once infection ruled out	Increase in 4-6 stools per day over baseline, moderate increase in ostomy output, IV fluids indicated <24 hours, not affecting ADLs; hold CPI, can consider restarting PD-L1/PD-1 once recovered to grade 1, permanently discontinue CTLA-4; rehydrate; supportive care with anti-diarrheals once infection ruled out, start corticosteroids, consult gastroenterology	Increase in $\geq$ 7 stools per day over baseline, incontinence, requiring IV fluids >24 hours, requiring hospitalization, severe increase in ostomy output; hold CPI, can consider restarting PD-L1/PD-1 once recovered to grade 1, permanently discontinue CTLA-4; admit to hospital if requiring IV rehydration and electrolyte repletion; start corticosteroids, consult gastroenterology, consider non-corticosteroids if required	Life-threatening complications, urgent intervention required; permanently discontinue CPI; admit to hospital for IV rehydration and electrolyte repletion; start IV corticosteroids, consult gastroenterology and general surgery, consider non-corticosteroids if no improvement

## **Gastrointestinal: Treatment and Monitoring Recommendations**

1. Management should be according to severity of symptoms after other causes are effectively ruled out.
2. Grade 1 symptoms should be treated with supportive measures, using anti-diarrheal agents and electrolyte replacement if needed. Safe to continue CPI with close monitoring of symptoms and hydration status. Alternatively, can hold and resume if toxicities do not exceed grade 1.
3. If symptoms are grade 2, hold CPI. Rehydrate as necessary with IV fluids. Treat with anti-diarrheal agents once infection has been ruled out. Assess need for hospitalization. If oral intake is possible, treat with oral corticosteroids at prednisone 1mg/kg/day of equivalent. When symptoms improve to grade 1 or less taper steroids slowly over 4-6 weeks. Can consider restarting PD-L1/PD-1 once recovered to grade 1, permanently discontinue CTLA-4 agent.
4. In patients with grade  $\geq 3$  diarrhea hold CPI. Admit to hospital. Supportive therapy including administration of IV fluids and anti-diarrheal agents once infection has been ruled out. Assess abdomen for any acute features. Treat with antibiotics of suspicion of SIRS/sepsis/perforation. High dose corticosteroids given intravenously at 1-2mg/kg/day. Those who respond within 3-5 days should be switched to the oral form and tapered over 6-8 weeks. Patients who do not respond to high-dose corticosteroids within 3-5 days should be switched to infliximab at a dose of 5-10 mg/kg. A single dose is typically sufficient with a rapid response (1-3 days), but patients may require a second dose 2 weeks after initial administration if symptoms are not resolved.<sup>24</sup> In the setting of grade 3 diarrhea restarting PD-L1/PD-1 once recovered to grade 1 can still be considered with significant caution, permanently discontinue CTLA-4 agent. In grade 4 toxicity, permanently discontinue CPI.

*Note: contraindications to infliximab include severe infection, TB, hypersensitivity to drug, and moderate to severe congestive heart failure.<sup>27</sup>*

5. Where prolonged corticosteroid treatments are used, consider PJP prophylactic antibiotics, proton pump inhibitors, calcium, and Vitamin D.

## **Hepatic: Prevention Recommendations**

1. Recommend careful patient selection. An underlying diagnosis of chronic hepatitis is not an absolute contraindication to therapy with PD-1/PD-L1 inhibition.<sup>28</sup>

## **Hepatic: Anticipation Recommendations**

1. Complete bloodwork including serum transaminases and bilirubin measurement prior to every cycle of therapy.
2. Immune-mediated hepatitis is typically asymptomatic and discovered on routine bloodwork. Hepatic toxicity is seen in ~5-10% of patients treated with anti-PD-1/PD-L1 and anti-CTLA-4 monotherapy and 1-2% of this is  $\geq$  grade 3 in severity. When these drugs are used in combination, the incidence of hepatitis increases to ~25-30%, ~15% of this is  $\geq$  grade 3 in severity.<sup>29,30</sup>

3. Although most patients are asymptomatic from immune-mediated hepatitis, note any potential symptoms of hepatitis including fever, right upper quadrant pain, and nausea. Counsel patients to inform their health care provider if they develop symptoms of jaundice, drowsiness, dark urine, increase in bruising/bleeding.

### Hepatic: Detection Recommendations

1. If serum transaminase elevation is noted, complete a careful assessment of potential causes including drugs (prescription, OTC including Tylenol, herbals), alcohol use, viral causes, and disease progression.
2. Liver biopsy is not typically required but may be considered in the case of severe hepatitis of unclear etiology.

**Table 5.** National Cancer Institute's CTCAE Classification for Liver Toxicity (Version 3)

Grade 1	Grade 2	Grade 3	Grade 4
Asymptomatic; AST or ALT <3 ULN and/or bilirubin <1.5 ULN	Asymptomatic; AST or ALT 3-5X ULN and/or bilirubin 1.5-3X ULN	Symptomatic liver dysfunction, compensated cirrhosis, reactivated hepatitis; AST or ALT 5-20X ULN and/or bilirubin 3-10X ULN	Decompensated liver function (ascites, coagulopathy, encephalopathy); AST or ALT >20X ULN and/or bilirubin >10X ULN

### Hepatic: Treatment and Monitoring Recommendations

1. Management should be according to severity of symptoms ensuring that other potential causes are effectively ruled out.
2. Grade 1 elevation in transaminases warrants close follow-up of bloodwork on a once or twice weekly basis. CPI can be continued. Avoid hepatotoxic drugs.
3. Grade 2 elevation of transaminases or bilirubin should lead to holding of CPI. Avoid hepatotoxic drugs. Bloodwork including liver enzymes and bilirubin should be repeated twice weekly to ensure resolution. If liver enzymes do not resolve following 1-2 weeks or with any symptoms, patients should be treated with oral corticosteroids at a dose of 0.5-1mg/kg/day prednisone (or equivalent). Taper steroids slowly over 4-6 weeks. Can consider resuming CPI if there is resolution of liver enzymes to grade 1 or less and on prednisone <10mg/day.
4. For ≥grade 3 elevation in liver enzymes or bilirubin, CPI therapy should be permanently discontinued. Patients should be treated with steroids methylprednisolone 1-2mg/mg/day. If there is no response within 2-3 days, mycophenolate mofetil (MMF) at a dose of 1000mg twice daily or azathioprine should be added. Infliximab is a less attractive option given the potential risk of idiosyncratic liver failure (no clear evidence of liver failure from other studies). Consult with a hepatologist. Liver biopsy may be necessary in cases of steroid and MMF refractory hepatitis. Patients require a slow taper over 4-6 weeks with potential re-escalation if required. The optimal duration of therapy is not clear.

- Where prolonged corticosteroid treatments are used, consider PJP prophylactic antibiotics, proton pump inhibitors, calcium, and Vitamin D.

### Endocrine: Prevention Recommendations<sup>1,31</sup>

- At this time, there is insufficient evidence to recommend screening with antibodies to predict which patients are going to be more susceptible to CPI-related endocrine complications. There is no role for pre-treatment with anti-inflammatory dose glucocorticoids to prevent the autoimmune endocrinopathies associated with CPI therapy.

### Endocrine: Anticipation Recommendations<sup>1,19,31-36</sup>

- Be aware of the potential immune-related endocrine adverse events (irEAE) that can occur with the use of CPIs. It is essential to identify these potential complications early, given the significant morbidity and mortality risk. Endocrine toxicities typically have non-specific symptomatology and endocrinopathies are often long lasting.
- Although the relative frequency of adverse events may vary between agents, in broad groups, hypophysitis (inflammation of the pituitary leading to dysfunction of pituitary hormone secretion and end-organ insufficiency), thyroid disorders (both hypo- & hyperthyroidism), autoimmune diabetes, and adrenalitis (primary adrenal insufficiency) are largely the endocrine complications seen with these drugs.
- Table 6 lists the details on endocrinopathy prevalence with various CPI agents. In addition to the difference in prevalence of endocrinopathy with each CPI agent, it seems that the risk of endocrine side effects vary between tumour groups. The risk of CPI-induced endocrinopathy seems to be increased in the presence of pre-existing organ-specific autoimmune disease and a family history thereof. However, this does not constitute a contraindication to the use of CPIs. It seems that CTLA4 agents and combination CPI therapy (simultaneous or sequential) have the highest rates of associated endocrinopathy. The presented data are approximate based on both clinical trials and clinical experience, they will vary further based upon tumour group, agent and patient comorbidities.

**Table 6.** Spectrum of Endocrinopathies Associated with Immune Checkpoint Inhibitor Therapy.\*

Agent	Hypophysitis	Thyroid	Autoimmune Diabetes	Adrenalitis
atezolizumab (Tecentriq)	0.2-4.2% 12-16 weeks	2.5-4% (0.3%) 12 weeks	<1%	0.5% 12 weeks
ipilimumab (Yervoy)	5-17% (3-7%) 4-16 weeks	0-4% (0.2%) 8-10 weeks	<1%	0.3-1.5% (0%) 12 weeks

Agent	Hypophysitis	Thyroid	Autoimmune Diabetes	Adrenalitis
nivolumab (Opdivo)	0.5% (0%) 13 weeks	5-9% (0.5%) 8-10 weeks	<1%	2% (0%) 12 weeks
pembrolizumab (Keytruda)	0.5-1% (0.1%) 12 weeks	5-15% (0.5%) 8-10 weeks	<1%	1% 12 weeks

\*The overall incidence is reported as a mean percentage from both primary clinical trial data and single institution series. The incidence of grade 3/4 toxicities is listed in parentheses. The median time to development of the complication are listed in months.

4. Identification of these clinical presentations can be challenging, given that they are often very non-specific. Consequently, a treating clinician should have a high level of suspicion for irEAEs when evaluating patients on CPIs. Patients need to be counselled on the significance of symptoms that indicate the above endocrine complications. The difficulty lies in that many of the symptoms are non-specific and overlap with symptoms from the underlying tumour, CPI therapy and other non-endocrine side-effects. Due to this, a treating clinician should be aware to have a low threshold to investigate with laboratory investigations and imaging.
5. Patients should be advised to monitor for the following symptoms: new onset or persistent headaches, visual changes, palpitations, excess sweating, extreme fatigue or weakness, dizziness or episodes of fainting, change in weight (gain or loss), muscle aches, salt craving, notable behaviour changes, polyuria, polydipsia, nausea, vomiting, or abdominal pain. Details of the more specific symptoms and signs are included in Table 7.

**Table 7.** New Onset Symptoms or Clinical Signs that can Indicate the Onset of CPI-Associated Endocrinopathy

	Hypophysitis	Hyperthyroid	Hypothyroid	Autoimmune Diabetes	Adrenalitis
Symptoms	headache, fatigue, muscle weakness, anorexia, double vision, confusion, polyuria/-dipsia	diarrhea, anxiety, muscle weakness, weight loss,	constipation, asthenia, weight gain	polyuria, polydipsia polyphagia + weight loss abdominal pain/confusion (DKA)	postural dizziness, abdominal pain, asthenia, weight loss
Specific signs	dehydration, Visual field and extra-ocular movement abnormalities, signs associated with hypothyroidism and -adrenalism	proximal muscle weakness, brisk reflexes, lid lag/thyroid stare, tachycardia, mild fever	peripheral edema, delayed relaxation of Deep tendon reflexes, bradycardia, hypothermia	Kussmaul's breathing (DKA), dehydration	orthostatic hypotension, hyper-pigmentation

### Endocrine: Detection Recommendations<sup>1,19,31-36</sup>

1. Given the prevalence of the side effects, it is reasonable to screen patients on therapy at every clinic visit. It is recommended that baseline levels of thyroid hormone (TSH), blood glucose, electrolytes be done before each treatment cycle. Subsequent thyroid function tests should be



measured during treatment, (e.g. every 4 weeks during the first 6 months then every 3 months for 6-12 months, then every 6 months subsequently). Blood glucose should be monitored with each treatment cycle during induction for 12 weeks, then every 4-6 weeks thereafter. The remainder of imaging and extended laboratory investigation can be completed on a symptom-driven/clinical exam basis. Consider monitoring with baseline early-morning ACTH and cortisol levels at baseline. It is important to assure that the end-organ hormones be ordered in the case of hypophysitis.

2. Specific endocrine organ testing as clinically indicated:

- Hypothyroidism (primary): TSH, fT4
- Hyperthyroidism: TSH, fT4, TSH receptor antibodies in patients who have clinical features of Grave's disease (e.g. ophthalmopathy)
  - in patients with hyperthyroidism, monitor TSH and fT4 every 2 to 3 weeks after diagnosis as patients can develop transient thyroiditis which is then followed by hypothyroidism
- Adrenalitis (primary): electrolytes, AM serum cortisol, ACTH, blood glucose
  - primary and secondary adrenal insufficiency can be distinguished by the relationship between ACTH and cortisol
  - if primary adrenal insufficiency is discovered biochemically evaluate for underlying cause of crisis (e.g. infection), consider adrenal CT for metastases/hemorrhage
  - patients on corticosteroids for management of other conditions will have low morning cortisol as a result of iatrogenic, secondary adrenal insufficiency
- Autoimmune diabetes: glucose, hemoglobin A1c, urine ketones, osmolality, anion gap, consider antibodies for autoimmune diabetes
- Hypophysitis: electrolytes, paired urine & serum osmolality, AM serum cortisol, ACTH, TSH, fT4, consider prolactin, consider MRI sella in patients with multiple endocrine abnormalities and complaints of new headaches, vision changes
  - it is important to note that several pituitary hormones are suppressed with acute illness
  - detection and replacement of sex steroids and growth hormone are long term consideration and thus, do not need to be measured in the acute setting

3. It is important to differentiate between primary and secondary hormonal abnormalities as this has implications for treatment.

4. Once confirmed, the grade of the adverse event should be scored as listed in Table 8 (adapted from the National Cancer Institute's CTCAE Classification). Grade 5 toxicity is defined as death.

5. Ultimately, early involvement of endocrinology can help to guide testing, replacement and appropriate monitoring.

**Table 8.** National Cancer Institute’s CTCAE Classification for Selected Endocrine Toxicities of CPI Therapy

Endocrinopathy	Grade 1	Grade 2	Grade 3	Grade 4
Hyperthyroidism	Asymptomatic or mild symptoms; clinical or diagnostic observations only; follow-up with FT4 q2-3 weeks to assess whether there will be persistent hyperthyroidism or hypothyroidism, intervention not indicated	Symptomatic; limiting IADLs, thyroid suppression therapy indicated; consider holding CPI until symptoms resolved, endocrine consultation, beta-blocker for symptoms	Severe symptoms; limiting self-care ADL; hospitalization indicated, endocrine consultation, beta-blockers, if signs of thyroid storm, hospitalize patient and initiate prednisone 1-2mg/kg/d, hold CPI until symptoms resolved	Severe symptoms; medical intervention or hospitalization indicated, endocrine consultation, beta-blockers, if signs of thyroid storm, hospitalize and initiate prednisone 1-2mg/kg/d, consider methimazole or PTU, hold CPI until symptoms have resolved
Hypothyroidism	Asymptomatic; TSH<10mIU/L, clinical or diagnostic observations only; intervention not indicated	Moderately symptomatic; able to perform BADLs, TSH persistently >10 mIU/L (measured 4 weeks apart), thyroid replacement indicated with TSH monitoring q6-8 weeks, hold CPI until symptoms resolved	Severe symptoms; limiting BADLs medical intervention or hospitalization indicated, endocrine consultation, consider IV therapy and ICU admission if signs of myxedema, thyroid replacement, hold CPI until symptoms resolved	Life threatening consequences; urgent intervention indicated, endocrine consultation, consider IV therapy and ICU admission if signs of myxedema, thyroid replacement, hold CPI until symptoms resolved
Adrenal Insufficiency	Asymptomatic or mild symptoms; consider holding CPI until patient is stabilized on replacement hormones, endocrine consult	Moderate symptoms; consider holding CPI until patient is stabilized on replacement hormones, endocrine consult	Severe or medically significant symptoms limiting ADLs; medical intervention or hospitalization indicated; urgent hospitalization for fluid resuscitation, IV stress-dose corticosteroids	Life threatening consequences; urgent intervention indicated; urgent hospitalization for fluid resuscitation, IV stress-dose corticosteroids
Hypophysitis	Asymptomatic or mild symptoms; considering holding CPI until patient is stabilized on replacement hormones, endocrine consult	Moderate symptoms; no limitation of ADLs, considering holding CPI until patient is stabilized on replacement hormones, endocrine consult	Severe or medically significant but not immediately life-threatening disabling limiting ADLs; hospitalization or prolongation indicated, hold CPI until patient is stabilized on replacement hormones, consider pulse dose prednisone 1-2 mg/kg oral daily (or equivalent) tapered over at least 1-2 weeks	Life threatening consequences; urgent intervention indicated; hospitalization indicated, hold CPI until patient is stabilized on replacement hormones, consider pulse dose prednisone 1-2 mg/kg oral daily (or equivalent) tapered over at least 1-2 weeks
Diabetes	Asymptomatic or mild symptoms; FBG > ULN, no laboratory evidence of T1DM; can consider oral therapy for T2DM, screen for T1DM, can continue CPI with close monitoring	Moderate symptoms; no limitation of ADLs; FBG >8.9-13.9 mmol/L, ketosis of any evidence of T1DM; hold CPI until glucose controlled, endocrinology consult, may require insulin	Severe symptoms; medically significant consequences; limitations in performing ADLs; FBG > 13.9-27.8 mmol/L, hold CPI until glucose controlled to grade 1 or less, endocrinology consult, admit for inpatient management, will require insulin	Severe symptoms; medically significant consequences; limitations in performing ADLs; FBG >27.8 mmol/L, hold CPI until glucose controlled to grade 1 or less, endocrinology consult, admit for inpatient management, will require insulin

These recommendations are moderate strength based on expert consensus, benefits outweighing harms.

## Endocrine: Treatment Recommendations<sup>1,8,31,33-37</sup>

1. With the need for ongoing CPI therapy, treatment of endocrine complications should happen with the involvement of an endocrinologist experienced in the management of these complications.
2. Endocrine adverse event specific recommendations:
  - **Hypothyroidism:** for thyroid replacement in patients without risk factors full replacement with thyroxine can be estimated at 1.6mcg/kg/d (synthroid or eltroxin are the most common preparations). If the patient is elderly or has significant comorbid cardiac disease, consider 30% replacement dose and a slower titration to normal TSH target.
    - If adrenal dysfunction is present, this must always be replaced before thyroid hormone therapy is initiated.
  - **Hyperthyroidism:** For severe hyperthyroidism/concern for thyroid storm: beta blockade, propylthiouracil, steroids (prednisone 1-2mg/kg/d or equivalent), followed by KI solution in an ICU/high observation unit monitored setting is suggested. For less severe forms of hyperthyroidism, methimazole (doses between 5-20 mg daily depending on the biochemistry) may be all that is needed.
  - **Diabetes:** Insulin can be used in any case of hyperglycemia in connection with a diabetes education service for support and titration of doses to glycemic target. A basal bolus insulin regimen should be initiated in the setting of autoimmune diabetes.
  - **Adrenal Insufficiency:** For adrenal replacement, glucocorticoid replacement maintenance with prednisone 5-10 mg daily or hydrocortisone 10 mg twice daily for grade 1. Patients may require mineralocorticoid replacement using fludrocortisone in the setting of primary adrenal insufficiency which is delivered as 0.1mg/day. Titrate based on symptoms. For outpatient management of acute symptoms of grade 2 adrenal insufficiency initiate at two to three times maintenance (if prednisone, 20 mg daily; if hydrocortisone, 20-30 mg twice daily to manage acute symptoms. Taper stress-dose corticosteroids down to maintenance doses over 5-10 days. For grade 3 or 4 adrenal insufficiency urgent hospitalization is required for fluid resuscitation, and IV stress-dose steroids (hydrocortisone 100 mg or dexamethasone 4 mg [if no confirmed diagnosis as this will not affect stimulation testing]). Taper down to maintenance doses over 7-14 days after discharge.
    - *Patient education is crucial. All patients must have education as well as obtaining a medical alert bracelet to trigger stress dosing in the setting on illness, surgery, etc.*

- **Hypophysitis:** Hypophysitis can affect the anterior pituitary, the posterior pituitary or both. Involvement of the posterior pituitary induces diabetes insipidus. Involvement of the anterior pituitary can cause secondary adrenal insufficiency, secondary hypothyroidism, secondary hypogonadism and growth hormone deficiency. These pituitary hormone deficiencies can occur synchronously or metachronously. From an acute management perspective, ADH and cortisol deficiencies are the most critical to diagnose and treat. Corticosteroids should be initiated first when planning hormone replacement therapy for multiple deficiencies. Thyroid replacement follows next in terms of clinical urgency. **Initiate corticosteroids several days before thyroid supplementation to prevent adrenal crisis.** Detection and replacement of sex steroids and growth hormone are long term considerations. Thus, these do not need to be measured in the acute setting. Given the effect of illness on both gonadal steroid and growth hormones, routine replacement is beyond the scope of these guidelines.

### **Endocrine: Monitoring Recommendations**<sup>1,8,31</sup>

1. Once identified, the hormone replacement can be achieved and managed throughout the duration of the CPI therapy. It has also been recommended to continue to screen for the symptoms of endocrinopathy after treatment has been completed. This can be accomplished by the routine lab panel being performed q3 months for the first year, q6 months for the second year and symptom-guided thereafter. Follow FT4 for thyroid hormone replacement titration (TSH is not accurate).
2. Unlike the resolution of many CPI immune-related adverse effects, the endocrine insufficiencies are more likely to be permanent, especially hypothyroidism.
3. For many of the non-endocrine immune-mediated toxicities (grade 2-4), anti-inflammatory doses of steroids are recommended to be given. As long as the steroid dose is greater than 10 mg/day of prednisone (or equivalent), the potential for co-existing adrenal insufficiency is moot as adrenal replacement is already being adequately achieved. However, once the dose is below this threshold, there is a potential concern for iatrogenic hypothalamic-pituitary-adrenal (HPA) axis suppression and illness management should be considered until the integrity of the HPA axis has been assessed.

### **Neurology: Prevention Recommendations**<sup>29,30,38-43</sup>

1. At this time, it is not possible to accurately predict which patients are going to be more susceptible to immune-related neurologic adverse events (irNAEs). There is no role for baseline serology, imaging, or other neurology testing.
2. Patients with pre-existing neurologic conditions, such as myasthenia gravis (MG), multiple sclerosis, or Guillain-Barre syndrome (GBS), should be closely monitored both by the treating medical oncologist and neurologist. There is no role for pre-treatment with anti-inflammatory dose

glucocorticoids to prevent irNAEs with CPI therapies. However, a low threshold for the initiation of an irNAE workup and empiric treatment must be maintained.

**Neurology: Anticipation Recommendations**<sup>1,32</sup>

1. Be aware of the potential immune-related neurological adverse events (irNAE) that can occur with the use of CPIs. Although irNAEs are rare in patients treated with CPIs, it is essential to identify these potential complications early, given the significant morbidity and mortality risk.
2. The relative frequency of adverse events may vary between agents, but irNAE can affect both the central and peripheral nervous systems. Potential neurological adverse events include: immune-mediated polyneuropathies (e.g. acute inflammatory demyelinating polyneuropathy (AIDP), GBS, chronic immune demyelinating polyneuropathy (CIDP), other sensory and motor neuropathies), enteric neuropathy, MG, aseptic meningitis, autoimmune encephalitis, transverse myelitis, and ocular inflammatory toxicity. Although these adverse events may occur at any time during treatment, the most common time to onset appears to typically occur between 6 to 13 weeks.<sup>17</sup>
3. Identification of these clinical presentations can be challenging, given that they are often very non-specific. Consequently, a treating clinician should have a high level of suspicion for irNAEs when evaluating patients on CPIs. Although the data on irNAE incidence rates from individual agents is limited (see Table 9), a high level of suspicion for irNAEs must be maintained when evaluating patients on CPIs. Patients should be counselled on the significance of symptoms that can indicate irNAEs. Details of the more specific symptoms and signs are included in Table 10.
4. Patients should be advised to monitor for the following symptoms: numbness/tingling in hands/feet, severe muscle weakness/fatigability, headache, fever, confusion, changes in mood/behavior, extreme sensitivity to light, neck stiffness, hallucinations, seizure, blurry/double vision, eye pain/redness.

**Table 9.** Spectrum of irNAEs Associated with Immune Checkpoint Inhibitor Therapy.\*

Agent	Immune-Mediated Polyneuropathies (Peripheral Motor/Sensory Neuropathy)	Acute Inflammatory Demyelinating Polyneuropathy (Guillain-Barre Syndrome)	Autoimmune Meningitis or Autoimmune Encephalitis
atezolizumab (Tecentriq)	≤1%	≤1%	≤1%
ipilimumab (Yervoy)	<1%	2 cases	<1%
nivolumab (Opdivo)	N/A	N/A	N/A
pembrolizumab (Keytruda)	1.7%	N/A	N/A

\*The overall incidence is reported as a mean percentage from both primary clinical trial data and single institution series.

**Table 10.** New Onset Symptoms or Clinical Signs that can Indicate the Onset of CPI-Associated Autoimmune irRAEs.

	CIDP or AIDP (GBS)	Myasthenia Gravis	Autoimmune Meningitis	Autoimmune Encephalitis
Symptoms	progressive weakness, gait instability, shortness of breath, facial nerve palsies, paresthesias, decreased sensation, dysesthesias	fluctuating muscle weakness and fatigue, shortness of breath, dysarthria, dysphagia, diplopia, ptosis	fever, headache, nausea, photophobia, nuchal rigidity, mental status should be preserved (differentiates from encephalitis)	altered mental status, headaches, seizures, focal neurological deficits (i.e. hemiparesis, cranial nerve palsy, etc.)
Specific signs	decreased symmetric strength, hyporeflexia, cranial nerve/bulbar abnormalities, tachycardia, dysautonomia diminished sensory, tremor	fatiguable weakness, positive tensilon and ice pack test, cranial nerve and bulbar abnormalities, hypoxia	jolt accentuation, , fever, kernig's sign, brudzinski's sign	decreased level of consciousness, fever, seizure

### Neurology: Detection Recommendations <sup>42-49</sup>

1. Given the potential for serious irNAE complications, as well as their non-specific clinical presentations, clinicians should monitor patients for signs and symptoms suggestive of acute and subacute polyneuropathies (including AIDP), MG, enteric neuropathy, meningitis, encephalitis, and ocular inflammatory toxicity. No routine screening investigations are indicated, unless there is clinical suspicion. Imaging and extended laboratory investigation should be completed on a clinical basis. Rule out progression of underlying malignancy, seizures, infectious processes, and metabolic derangement as causes of neurological impairment.
2. Early involvement of a neurologist is recommended to guide specific testing.
3. AIDP can present with symmetrical, progressive weakness and paresthesias. In low grade 1-2, it can manifest with mildly affected mobility/gait limitations. In severe grade  $\geq 3$  GBS, weakness may affect respiratory muscles and facial oculomotor and oropharyngeal muscles, dysautonomia, and diminished reflexes may be identified. The following should be performed if there is clinical suspicion of GBS:
  - Urgent neurological consultation is necessary.
  - Prompt exclusion of other potential causes of weakness. This may require MRI to rule out a compressive lesion and evaluate for nerve root enhancement/thickening.
  - Lumbar puncture may be performed. CSF can show high protein and normal to elevated white blood cell counts in patients with classic GBS. Cytology should be sent on any CSF sample in patients with cancer.
  - Electromyography (EMG) and nerve conduction studies (NCS).
  - Pulmonary function testing with negative inspiratory force and vital capacity.

*Note: all grades require work-up and intervention given the potential for progression and risk of respiratory compromise.*

4. MG may present with fluctuating and fatigable muscle weakness. Weakness often affects the bulbar, ocular, limb, and respiratory muscles. Classically, ptosis, diplopia, dysarthria, and dysphagia may be encountered. If there is clinical suspicion of MG of **any grade**, the following should be performed:
  - Urgent neurological consultation is necessary
  - Bedside tests have high false-positivity, but the tensilon and ice-pack test, may be performed
  - EMG and NCS
  - Autoantibody serum testing for acetylcholine receptor (AChR-Ab). If AChR-Ab are negative, muscle specific tyrosine kinase (MuSK-Ab) may be sent
  - Creatinine phosphokinase (CPK), ESR, CRP, for concomitant myositis
  - Pulmonary function assessment with negative inspiratory force and vital capacity

*Note: all grades require work-up and intervention given the potential for progression and risk of respiratory compromise.<sup>50</sup>*

5. Autoimmune meningitis (aseptic meningitis) is characterized by fever, nuchal rigidity, and altered mental status. The following should be performed if there is clinical suspicion of meningitis:
  - Brain imaging
  - Urgent blood cultures and lumbar puncture (should see normal glucose, negative gram stain and cultures)
  - Urgent administration of IV antibiotics and acyclovir
6. Encephalitis often presents with altered mental status, seizures, focal neurological deficits (e.g. hemiparesis, cranial nerve palsy, etc.). The following should be performed if there is clinical suspicion of encephalitis:
  - Urgent brain imaging
  - Urgent blood cultures, viral studies, and lumbar puncture (cell count, protein, glucose and Gram stain, culture, PCR for HSV and other viral PCRs depending on suspicion, cytology)
  - Urgent administration of IV antibiotics and acyclovir

**Table 11. Grading System for Selected Neurological Toxicities of CPI Therapy**<sup>42,43,49</sup>

irNAE	Grade 1	Grade 2	Grade 3	Grade 4
Peripheral Motor/Sensory Neuropathy	Asymptomatic or mild symptoms; clinical or diagnostic observations only; continue immunotherapy; intervention not indicated (consider neurology referral)	Moderate Symptoms limiting ADL's; withhold immunotherapy until grade 1; medical intervention indicated (e.g. gabapentin, pregabalin, duloxetine), prednisone at 0.5-1 mg/kg/day may be initiated, with slow taper once improved	Severe symptoms; permanently discontinue immunotherapy; hospitalization indicated, medical therapy with IV steroids as per GBS management, urgent neurology referral	Life threatening consequences; urgent intervention indicated, hospitalization, medical therapy with IV steroids, urgent neurology referral
Aseptic Meningitis	Mild symptoms, no interference with function Empiric antiviral (IV acyclovir) and antibiotics until CSF results. Once bacterial and viral infection negative, may closely monitor off corticosteroids or start oral prednisone 0.5-1 mg/kg. Hold CPI and discuss risk and benefits with patient	Moderate symptoms, some interference with ADL. Empiric antiviral (IV acyclovir) and antibiotics until CSF results. Once bacterial and viral infection negative, may closely monitor off corticosteroids or start oral prednisone 0.5-1 mg/kg. Hold CPI and assess risk and benefits	Focal neurological deficit/abnormality; withhold immunotherapy; hospitalization indicated; empiric antiviral (IV acyclovir) and antibiotics until CSF results; once bacterial and viral infection negative, may closely monitor off corticosteroids or start oral prednisone 0.5-1 mg/kg	Life threatening consequences; urgent intervention indicated; empiric antiviral (IV acyclovir) and antibiotics until CSF results; once bacterial and viral infection negative, may closely monitor off corticosteroids or start oral prednisone 0.5-1 mg/kg or or IV methylprednisolone 1 mg/kg
Encephalitis	For all grades of encephalopathy hold ICPI and discuss resumption only after taking into account the risks and benefits, empiric antiviral (IV acyclovir) and antibiotics until CSF results, trial of methylprednisolone 1-2 mg/kg and if no improvement in 24 hours, consider pulse methylprednisolone 1g IV daily for 3-5 days plus IVIG 2g/kg over 5 days, if no improvement, consider escalation to rituximab			
Myasthenia Gravis	Asymptomatic or mild symptoms; clinical or diagnostic observations only; urgent neurology referral	Moderate Symptoms limiting ADLs; withhold immunotherapy; medical intervention indicated, oral prednisone 0.5-1 mg/kg	Severe, limiting ADLs, any dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms, discontinue CPIs; urgent neurology consultation, hospitalization indicated (may need ICU monitoring), IV methylprednisolone 1 mg/kg and initiate IVIG or plasmapheresis, pulmonary function monitoring	Life threatening consequences; discontinue CPIs; urgent neurology consultation, urgent intervention indicated (may need ICU monitoring), IV methylprednisolone 1 mg/kg and initiate IVIG or plasmapheresis, pulmonary function monitoring
Guillain-Barre Syndrome (GBS)	For all grades of GBS, discontinue ICPI admission to inpatient unit with capability of transfer to ICU-level of care, start IVIG or PLEX along with corticosteroids either methylpred 2-4 mg/kg or 1g daily x 5 days depending on severity, monitoring for pulmonary and concurrent autonomic neuropathy			



## **Neurology: Treatment and Monitoring Recommendations**<sup>32,42-46,48,49,51,52</sup>

1. Treatment of irAEs should occur with the involvement of a neurologist experienced in the management of these complications.
2. Grade  $\geq 2$  MG, meningitis, encephalitis, or AIDP should result in permanent discontinuation of CPI treatment. The oncologist may consider reinstating CPI in the setting of grade 1 maximum toxicity after assessing risk/benefits with the patient. The differential must remain broad, necessitating the previously mentioned investigations and initial treatment for severe causes until they are ruled out. In particular, infection must be ruled out. Urgent neurology consultation should be strongly considered to guide management; depending upon the etiology, methylprednisolone (e.g. encephalitis) or IVIG (e.g. AIDP) may be indicated. Other non-corticosteroid immunosuppressive agents may be considered.
3. Following the acute use of corticosteroids, a slow taper of corticosteroids must occur over a minimum of 1 month. Where prolonged corticosteroid treatments are used, consider PJP prophylactic antibiotics, proton pump inhibitors, calcium, and Vitamin D.
4. In grade 1-2 irNAEs (not including MG, meningitis, encephalitis, or AIDP), re-initiation of CPI therapy may be considered once grade 0-1 is achieved, the steroid dose is  $\leq 10$  mg/day of a prednisone equivalent, and there is no need for a non-corticosteroid immunosuppressant. Close monitoring is necessary for recurrence or worsening of irNAEs.
5. Grade  $\geq 3$  irNAEs must result in the discontinuation of CPI therapy. MG, meningitis, encephalitis, or AIDP of any grade must also result in discontinuation of CPI therapy. A high clinical suspicion must be maintained for recurrence of these irNAEs.

## **Rheumatology: Prevention Recommendations**<sup>31,53,57</sup>

1. At this time, it is not possible to accurately predict which patients are going to be more susceptible to immune-related rheumatologic or autoimmune disorder adverse events (irRAEs). There is no role for baseline serology, imaging, or other testing.
2. There is no role for pre-treatment with anti-inflammatory dose glucocorticoids to prevent irRAEs with CPI therapies. However, a low threshold for the initiation of an irRAE workup and empiric treatment must be maintained. Patients with pre-existing autoimmune disorders should be closely monitored both by the treating medical oncologist and rheumatologist.

## Rheumatology: Anticipation Recommendations<sup>1,32,57</sup>

1. The first step in anticipation is to be aware of the potential immune-related rheumatologic or autoimmune disorder adverse events (irRAE). It is possible to exacerbate or unmask a rheumatologic condition with CPI therapies. It is important to note that patients with autoimmune disorders were excluded from the clinical trials investigating these CPI agents.
2. Patients should be counselled on the significance of symptoms that indicate the above irRAEs. Patients with pre-existing autoimmune disorders should be advised that it may be exacerbated by CPI therapy. Unfortunately, the identification of many of these clinical presentations is challenging, given the non-specific and general symptoms. Consequently, a treating clinician should be aware to have a low threshold to investigate with laboratory investigations and imaging. Details of the more specific symptoms and signs are included in Table 12. Patients should be advised to monitor for the following symptoms: painful or swollen joints, rash, weakness, muscle ache or pain, shortness of breath, cough, dry eyes and mouth.
3. The relative frequency of adverse events may vary between agents, but potential irRAEs may include: polymyalgia rheumatic (PMR), vasculitis, leukocytoclastic vasculitis, psoriasis, rheumatoid arthritis (RA), tenosynovitis, gout, polymyositis, myositis, ocular myositis, sarcoidosis, systemic lupus erythematosus (SLE), Behcets disease, scleroderma, Sjogren's, and erythema multiforme.
4. Data on irRAEs in CPI-treated patients is limited. Mild to moderate arthralgias are seen most commonly at an incidence of up to 40%.<sup>42,54,55</sup> Grade 3 irAEs are less commonly seen but can have a significant impact on quality of life. The most common musculoskeletal and rheumatic irAEs are arthritis, polymyalgia-like syndromes, and myositis<sup>50</sup>. Other irRAEs have also been described, including vasculitis, polymyositis, and temporal arteritis, but at a lower incidence.<sup>56</sup> Although these can occur with both anti-CTLA-4 and PD-1/PD-L1 agents, they occur more frequently with PD-1/PD-L1 inhibitors and with combination therapy.
5. Remain vigilant with patients on CPI therapy as irRAEs may occur at any time on treatment and even after treatment discontinuation.

**Table 12.** New Onset Symptoms or Clinical Signs that can Indicate the Onset of irRAE.

irRAE	Inflammatory Arthritis	Myositis	Polymyalgia Rheumatica	Sjogren's
Symptoms	Joint pain with associated swelling; inflammatory symptoms (AM stiffness or after inactivity lasting. 30 minutes to 1 hour)	Muscle inflammation with weakness and elevated muscle enzymes (CK). Muscle pain can be present in severe cases. Can be life threatening if respiratory muscles or	Marked proximal muscle pain and stiffness without true muscle weakness, systemic symptoms of fatigue, low grade fever	dry eyes and mouth, increased dental caries, increased parotid gland size

irRAE	Inflammatory Arthritis	Myositis	Polymyalgia Rheumatica	Sjogren's
		myocardium are involved		
Specific signs	painful boggy peripheral joints, symmetrical polyarthritis involvement, MCP/MTP joints, rheumatoid nodules	Objective muscle weakness, heart failure, respiratory failure	proximal muscle tenderness and stiffness, synovitis, bursitis, tenosynovitis, normal power, fatigue, low-grade fever	lacrima/parotid gland enlargement, oral caries and candida, positive Schirmer test, minimal sublingual salivary pooling

**Rheumatology: Detection Recommendations**<sup>1,32,44-49,51,57</sup>

- Given the potential for serious irRAE complications, as well as their non-specific clinical presentations, clinicians should monitor patients for signs and symptoms suggestive of irRAE conditions including; inflammatory arthritis, polymyositis, myositis, PMR, and be aware for the potential of developing vasculitis, psoriasis, sarcoidosis, SLE, Behcets disease, scleroderma, Sjogren's, and erythema multiforme.
- Inflammatory markers are usually very elevated in patients with irRAE and are useful to differentiate these events from other causes of their symptoms.
- Inflammatory arthritis:
  - Clinical presentation can vary, affecting large and/or small joints, can have extra-articular symptoms including rash, tenosynovitis, axial involvement, conjunctivitis and urethritis.
  - Complete a thorough history and physical exam with examination of all peripheral joints for swelling, pain, and range of motion.
  - Exclude other causes including septic arthritis, viral polyarthritis, gout.
  - Consider imaging of affected joints with plain film x-ray to evaluate for joint damage and rule out bony metastatic disease.
  - Consider serological testing including ANA, rheumatoid factor (RF), anti-citrullinated protein antibody (anti-CCP), and inflammatory markers erythrocyte sedimentation rate (ESR) and CRP. If symptoms are suggestive of reactive arthritis or affect the spine, consider HLA B27 testing.
  - Early recognition is critical to avoid erosive joint damage. Referral to a rheumatologist if there is evidence of joint swelling (synovitis) or if symptoms of arthralgia persist >4 weeks.
- Myositis:
  - Myositis is a rare but potentially fatal toxicity of CPIs. Patients most commonly present with weakness, primarily in the proximal extremities. In severe cases, can also have myalgia. It can have a fulminant necrotizing course with rhabdomyolysis and involve other skeletal muscle, such as myocardium which can be potentially fatal if treatment is delayed.

- Complete a thorough rheumatologic, neurologic, and dermatologic exam paying specific attention to symptoms of muscle weakness or rash.
- Complete blood testing for creatinine kinase (CK), transaminases (AST, ALT) and LDH, inflammatory markers (ESR, CRP). *There is no evidence that autoantibodies (anti-Jo, anti-Mi2) have a role in CPI-induced myositis.*
- Evaluate for other potential causes including drugs, alcohol, infectious, metabolic or electrolyte disorders.
- Consider troponin level to evaluate myocardial involvement as well as other cardiac investigations (e.g. echocardiogram) as required.
- Consider electromyography (EMG), imaging (MRI), and/or biopsy on an individual basis when diagnosis is uncertain.
- Consider paraneoplastic autoantibody testing for myositis and neurologic conditions, such as MG.
- Early referral to a rheumatologist if myositis is grade 2 or higher.

#### 5. Polymyalgia rheumatica:

- PMR presents as proximal myalgias and systemic symptoms including fatigue and low grade fever.
- Complete a thorough rheumatologic and neurologic examination.
- Assess for symptoms of temporal arteritis including headache, jaw claudication, vision loss, **and urgent temporal artery biopsy if this is suspected.**
- Complete blood testing for inflammatory markers (ESR, CRP) which are elevated in PMR, and investigations required for differential diagnosis; CK, ANA, RF, and anti-CCP (negative in PMR).
- Early referral to a rheumatologist if PMR is grade 2 or higher.

#### 6. Sjogren's syndrome:

- Can present with sicca symptoms including dry eyes and mouth, enlarged parotid gland, and non-glandular involvement including arthritis and vasculitis.
- Complete a thorough rheumatologic and dermatologic examination with assessment of the oropharynx for cracked tongue, lack of saliva pooling.
- Complete blood testing including serological markers such as ANA, ENA (anti-Ro/SSA and/or anti-La/SSB antibodies), RF, anti-CCP antibody as sicca symptoms can occur with SLE and RA.
- Early referral to a rheumatologist for considering of Schirmer test, minor salivary gland (lower lip) biopsy, sialometry.

#### 7. Sarcoid

- Most commonly seen with anti-CTLA4 or anti PD1 use in melanoma

- Presents as cutaneous sarcoidosis, or systemic with lymphadenopathy, lung or neurological and ocular involvement
- No specific serum findings
- May present with mediastinal or hilar lymphadenopathy on CT, but also parenchymal lung CT changes, such as ground glass opacities

8. Ultimately, early involvement of rheumatology can help to guide testing.

**Table 13.** Grading System for Selected Autoimmune or Rheumatologic Toxicities of CPI Therapy

irRAE	Grade 1	Grade 2	Grade 3	Grade 4
<b>Inflammatory Arthritis</b>	Asymptomatic or mild symptoms; (pain with inflammation, erythema, or joint swelling), clinical or diagnostic observations only; continue immunotherapy; intervention not indicated, analgesia (acetaminophen, NSAIDs); (consider rheumatology referral)	Moderate pain associated with symptoms, limiting IADLs; withhold immunotherapy; analgesia (acetaminophen, NSAIDs); medical intervention indicated initiate prednisone 10-20 mg/d or equivalent for 4-6 weeks, if no improvement treat as grade 3rheumatology referral	Severe pain associated with symptoms, limiting BADLs withhold immunotherapy; medical intervention or hospitalization indicated; initiate oral prednisone 0.5-1 mg/kg, if worsening or no improvement after 4 weeks, consider synthetic or biologic DMARD*, urgent rheumatology referral	Severe pain associated with symptoms, limiting BADLs, irreversible joint damage, life threatening consequences; urgent intervention indicated; urgent rheumatology referral
Polymyalgia Rheumatica	Asymptomatic or mild symptoms (stiffness and pain); clinical or diagnostic observations only; continue immunotherapy; intervention not indicated; analgesia (acetaminophen, NSAIDs); (consider rheumatology referral)	Moderate Symptoms limiting IADLs; withhold immunotherapy; medical intervention indicated; prednisone 20 mg/d or equivalent for 3-4 weeks, if no improvement treat as grade 3; rheumatology referral	Severe symptoms; withhold immunotherapy; medical intervention or hospitalization indicated; initiate prednisone 20-40 mg/d or equivalent, if no improvement or need for prolonged therapy, offer corticosteroid-sparing agent such as methotrexate or IL-6 inhibition, urgent rheumatology referral	Life threatening consequences; urgent intervention or hospitalization indicated; initiate prednisone 20-40 mg/d or equivalent, if no improvement or need for higher dosages for prolonged time, may offer corticosteroid-sparing agent such as methotrexate or IL-6 inhibition, urgent rheumatology referral
Myositis	Mild weakness with or without pain, clinical or diagnostic observations only; continue immunotherapy; analgesia (acetaminophen, NSAIDs); if CK is elevated and patient has muscle weakness treat as grade 2 (consider rheumatology referral)	Moderate weakness with or without pain, limiting IADLs, withhold immunotherapy; medical intervention indicated; 1) Prednisone 10-20mg/d or equivalent fo9r 4-6 weeks 2) If CK is >3x elevated initiate prednisone or equivalent at 0.5-1 mg/kg 3) may require permanent discontinuation of CPI in most patients with G2	Severe weakness with or without pain, limiting BADLs, withhold immunotherapy until grade 1 or less while off immune suppression, permanently discontinue if any evidence of myocardial involvement, hospitalization for severe weakness, prednisone 1 mg/kg or equivalent, urgent rheumatology referral Consider plasmapheresis, IVIG therapy or other	Severe weakness with or without pain, limiting BADLs, withhold immunotherapy until grade 1 or less off immune suppression, permanently discontinue if any evidence of myocardial involvement, hospitalization for severe weakness, prednisone 1 mg/kg or equivalent, urgent rheumatology referral Consider 1-2 mg/kg of methylprednisolone IV or higher-dose bolus if severe compromise

irRAE	Grade 1	Grade 2	Grade 3	Grade 4
		symptoms and objective findings (elevated enzymes, abnormal EMG, abnormal muscle MRI or biopsy) prednisone 20 mg/d or equivalent for 3-4 weeks, if no improvement treat as grade 3; rheumatology referral	immunosuppressant therapy, if symptoms and CK levels do not improve or worsen after 4-6 weeks	(weakness severely limiting mobility, cardiac, respiratory, dysphagia), Consider plasmapheresis, IVIG, other immunosuppressant therapy, if symptoms and CK levels do not improve or worsen after 4-6 weeks

\*test for viral hepatitis B, C, and latent/active TB test prior to DMARD treatment

### Rheumatology: Treatment and Monitoring Recommendations<sup>1,32,44-49,51,57</sup>

1. With the need for ongoing CPI therapy, treatment of rheumatologic complications should happen with the involvement of a rheumatologist experienced in the management of these complications.
2. Corticosteroids can be used as part of initial therapy in inflammatory arthritis as in other irAEs but due to likely prolonged treatment requirements, physicians should consider starting corticosteroid-sparing agents earlier than typically required with other irAEs.
3. Following the acute use of corticosteroids, a slow taper of corticosteroids must occur over a minimum of 1 month. Where prolonged corticosteroid treatments are used, consider PJP prophylactic antibiotics, proton pump inhibitors, calcium, and Vitamin D.
4. A number of other rheumatic disorders have been documented as case reports of patients receiving CPIs including vasculitis and lupus-like syndromes. Management and treatment principles are similar to those reported for other CPI-induced rheumatic syndromes.
5. It is recommended that all patients with inflammatory arthritis be monitored with serial rheumatologic examinations, including inflammatory markers, every 4 to 6 weeks after treatment is instituted.

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## Appendix A: Literature Search Details

The literature search performed included a PubMed search that was conducted on 2016 October 8. The following terms for immune checkpoint inhibitors, adverse events and cancer were used in the search.

((immune checkpoint inhibitor\*) OR ipilimumab OR pembrolizumab OR lambrolizumab OR nivolumab OR "Anti CTLA-4" OR "Anti CTLA 4" OR "Cytotoxic T-Lymphocyte Associated Protein 4" OR "PD-1" OR "PD-L1" OR "programmed cell death protein 1" OR IDO OR "indoleamine 2,3-dioxygenase" OR tremelimumab OR atezolizumab OR ticilimumab OR indoximod OR 1-methyl-d-tryptophan OR D-1MT OR MDX-010 OR MDX-101 OR BMS-734016 OR MK-3475 OR "SCH 900475") AND ("Drug-Related Side Effects and Adverse Reactions"[Mesh] OR "adverse events" OR toxicity) AND ("Neoplasms"[Mesh] OR oncolog\* OR cancer OR malignan\*)

This search was limited to humans and the English language. No restrictions were applied in regards to study type or publication year. Articles met inclusion criteria if they were peer-reviewed guidelines, reviews or studies that reported on the presentation and prevalence of irAEs, their monitoring, management or follow up. Case reports on the management of toxicities were excluded with the exception of those which were included in overarching reviews.

This search yielded 480 articles, of which 9 review articles (6 meta-analyses and 3 pooled analyses) with a focus on investigating checkpoint inhibitor therapy related toxicities in cancer patients were included for data extraction. Eleven studies (7 retrospective reviews, 3 retrospective observational studies, 1 randomized controlled trial and 1 secondary analysis of a phase III trial) were included, as well as 3 guidelines. These articles provided recommendations for the follow-up and management of immune-mediated adverse events.

Another aspect of the search included looking for existing guidelines on this topic that had already been published by prominent cancer associations, including the Canadian Partnership Against Cancer, the National Comprehensive Cancer Network and the American Cancer Society.

## Appendix B: Comparison of Systemic Corticosteroid Doses

Adapted from Uptodate (uptodate.com).

	Equivalent Dose (mg)	Antiinflammatory Activity Relative to Hydrocortisone*	Duration of Action (hr)
<b>Glucocorticoids</b>			
<b>Short Acting</b>			
Hydrocortisone (cortisol)	20	1	8 to 12
Cortisone acetate	25	0.8	8 to 12
<b>Intermediate Acting</b>			
Prednisone	5	4	12 to 36
Prednisolone	5	4	12 to 36
Methylprednisolone	4	5	12 to 36
Triamcinolone	4	5	12 to 36
<b>Long Acting</b>			
Dexamethasone	0.75	30	36 to 72
Betamethasone	0.6	30	36 to 72
<b>Mineralocorticoids</b>			
Fludrocortisone	Not used for an antiinflammatory effect**. They typical dose of fludrocortisone for mineralocorticoid replacement is 0.1 to 0.2 mg.		12 to 36

\*Equivalent antiinflammatory dose shown is for oral or intravenous (IV) administration. Relative potency for intraarticular or intramuscular administration may vary considerably.

\*\* The antiinflammatory potency is 10 to 15 times that of hydrocortisone; however, fludrocortisone is not used clinically as an antiinflammatory agent.

The mineralocorticoid effect of commonly administered glucocorticoids may be estimated as follows:

- When given at replacement doses, triamcinolone, dexamethasone, and betamethasone have no clinically important mineralocorticoid activity.
- 20 mg hydrocortisone and 25 mg of cortisone acetate each provide a mineralocorticoid effect that is approximately equivalent to 0.1 mg fludrocortisone.
- Prednisone or prednisolone given at antiinflammatory doses  $\geq 50$  mg per day provide a mineralocorticoid effect that is approximately equivalent to 0.1 mg of fludrocortisone.

## Development and Revision History

This guideline was reviewed and endorsed by members of the Alberta Provincial Tumour Teams, including medical oncologists, gynecologic oncologists, hematologists, nurse practitioners, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Tumour Teams, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the [Guideline Resource Unit Handbook](#).

This guideline was originally developed in 2020.

## Maintenance

A formal review of the guideline will be conducted in 2021. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

## Abbreviations

ACTH, adrenocorticotropic hormone; AChR-Ab, autoantibody serum testing for acetylcholine receptor; ADLs, activities of daily living; AIDP, acute inflammatory demyelinating polyneuropathy; ALT, alanine aminotransferase; ANA, antinuclear antibody; anti-CCP, anti-citrullinated protein antibody; anti-La/SSB, anti-Sjögren's-syndrome-related antigen B; Anti-RO/SSA, anti-Sjögren's-syndrome-related antigen A; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; BASDLs, basic activities of daily living; BSA, body surface area; CBC, complete blood count; CIDP, chronic immune demyelinating polyneuropathy; CMV, cytomegalovirus; CPIs, checkpoint inhibitors; CPK, creatinine phosphokinase; CRP, C-reactive protein; CSF, cerebrospinal fluid; CTCAE, common terminology for adverse events; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; DKA, diabetic ketoacidosis; DRESS, drug rash with eosinophilia and systemic symptoms; EMG, Electromyography; ESR, erythrocyte sedimentation rate; FBG, fasting blood glucose; fTe, free thyroxine; GBS, Guillain-Barre syndrome; GI, gastrointestinal; HCC, Hepatocellular carcinoma; HIV, human immunodeficiency virus; HNSCC, head and neck squamous cell carcinomas; HRT, hormone replacement therapy; HSV, herpes simplex virus; IADLs, instrumental activities of daily living; IgG, immunoglobulin G; irAEs, immune-related adverse effects; irDAEs, immune-related dermatologic adverse events; irEAE, immune-related endocrine adverse events; irPAEs, immune-related pulmonary adverse events; irNAEs, immune-related neurologic adverse events; irRAEs, immune-related rheumatologic or autoimmune disorder adverse events; IVIG, intravenous immune globulin; LDH, Lactate dehydrogenase; LFT, liver function test; mAb, monoclonal antibodies; MG, myasthenia gravis; MM, metastatic melanoma; MMF, mycophenolate mofetil; MuSK-Ab, muscle specific tyrosine kinase; NCS, nerve conduction studies; NSCLC, non-small-cell lung carcinoma; NSAIDs, nonsteroidal anti-inflammatory drugs; OTC, over the counter; PCR, polymerase chain reaction; PD-1, programmed cell death-1; PD-L1, programmed cell death-1 ligand; PJP, pneumocystis Jiroveci Pneumonia; PMR, polymyalgia rheumatic; QOL, quality of life; RA, rheumatoid arthritis; RCC, renal cell carcinoma; RF, rheumatoid factor; SIRS, systemic inflammatory response syndrome; SLE, systemic lupus erythematosus; SJS, Stevens-Johnson syndrome; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TB, Tuberculosis; TEN, toxic epidermal necrolysis; TNF $\alpha$ , tumour necrosis alpha; TSH, thyroid-stimulating hormone; ULN, upper limits of normal

## Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial Tumour Teams and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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## Conflict of Interest Statements

**Dr. Aurore Fife-Mah** has nothing to disclose.

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**Dr. Vicky Parkins** has nothing to disclose.

**Dr. Gloria Roldan Urgoiti** reports being a principal investigator on two clinical trials sponsored by Roche involving immunotherapy, but no direct compensation.

**Dr. Thomas Salopek** reports grants and personal fees from BMS, Merck, Novartis, and Abbvie outside of the submitted work, as well as personal fees from Johnson and Johnson, Bausch Health, Lilly, Amgen, Sanofi, EMD Serono, Celgene, and UCB outside of the submitted work.

**Dr. Michael Smylie** reports other fees from Bristol Myers, Merck, Novartis, and EMD Serono outside of the submitted work.

**Derek Tilley** has nothing to disclose.

**Dr. John Walker** has nothing to disclose.

**Dr. Steven Yip** reports other from BMS, other from Novartis, other from Pfizer, other from Hoffman-La Roche, grants and other from Janssen, grants and other from Bayerl, outside the submitted work.