Cancer Care Ontario

Immune Checkpoint Inhibitor Toxicity Management

Clinical Practice Guideline

Ontario
Cancer Care Ontario

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Introduction

Immune checkpoint inhibitors (ICIs) enhance the action of the immune system against tumour cells by blocking negative regulators of T-cells. Currently, the ICI medications available target CTLA-4 and PD-1/PDL1 receptors.

While this is effective in activating the immune system against tumour cells, it can lead to adverse events due to the disruption of immunologic homeostasis and the augmentation of immune system response.[1, 2] Immune-related adverse effects (irAEs) are different in their presentation, onset and duration compared to conventional chemotherapy. Initial irAE presentation can occur months after completion of treatment and affect multiple organs. If no other cause can be identified, irAEs should be considered and prompt treatment should be initiated.[1-11]

The combination regimen of CTLA-4 and PD-1 is indicated for metastatic melanoma, and is being studied in other disease sites. With combination treatment, irAEs are more common and severe (55% grade 3 or higher), develop earlier and may last longer than with monotherapy.[4,12]

TABLE 1 Examples of ICIs

IMMUNE CHECKPOINT INHIBITOR TYPE	EXAMPLE(S)
CTLA-4	ipilimumab
PD-1	pembrolizumab, nivolumab
PD-L1	atezolizumab, durvalumab, avelumab

Immune-related adverse effects

Dermatological toxicities

Dermatological toxicities are the most common type of irAE and typically present as a maculopapular rash and/or pruritus, but may have other presentations. Immune-related dermatological toxicities occur in 20 - 40% of patients, usually starting after the third week of therapy and peaking at the sixth week.[2,13] They may be persistent and extend over months to years. Dermatologic consultation is strongly advised in cases resistant to initial management. Rashes are typically grade 1 and occur on the limbs or trunk.[1,2] Other dermatological toxicities including vitiligo, bullous pemphigoid, psoriatic rashes, and severe reactions such as Stevens-Johnson syndrome have been reported.[1]

The main approach to treatment includes the use of topical or systemic corticosteroids and, if necessary, anti-pruritic supportive therapy, interruption or discontinuation of the ICIs, and a dermatology consultation. ICIs may be continued in mild to moderate cases.[1,2,4,13] Symptom management with the use of topical corticosteroids, along with supportive approaches like cold compresses, oatmeal baths, and systemic antihistamines may be necessary.[1,4,13] As the lesions become more severe and/or persistent, systemic steroids should be initiated, and dermatology consult and interruption of ICIs considered.[1,2,13]

Additional immunosuppressive medications should be considered when there is no response to systemic corticosteroids.[1] ICIs should be permanently discontinued if symptoms fail to improve, blisters develop, or if life-threatening complications such as Steven's Johnson Syndrome occur.[1,13] These cases also require hospital admission for supportive management with IV fluids, electrolyte replacement, and higher doses of corticosteroids.[1]

Vitiligo, though permanent, does not have nor require any treatment or necessitate discontinuation of therapy.[1,13] However, patients need to be aware that affected skin is susceptible to severe sun damage and appropriate precautions should be taken.[13] Detailed management of dermatological toxicities associated with ICIs is outlined in **Figure 1**.

Immune checkpoint inhibitor medications are effective treatments for many types of cancers, including melanoma, Hodgkin lymphoma, lung, renal, bladder, and head and neck cancers. They are actively being studied in many other cancer types as well.

Diarrhea and colitis

Diarrhea and colitis occur more frequently in patients on anti-CTLA-4 therapy than those on anti-PD-1/PDL1 therapy.[1,5,13] Approximately 30% of patients on anti-CTLA-4 will experience diarrhea with 4-8% experiencing diarrhea of grade 3 or higher.[5,10,13] Patients may also experience colitis, presenting with abdominal cramping; 2-5% of patients experience ≥ grade 3 colitis with mild diffuse bowel thickening or segmental colitis on imaging.[1,5,10] These symptoms have a median onset of 6-8 weeks after initiation of therapy and may become life-threatening if left untreated.[1,13] Other etiologies must be ruled out, including pathogens such as *C.difficile* and other bacterial or viral infections which can exist concurrently to irAEs.[15,16]

Diarrhea and colitis are treated similarly.[1] Management is dependent on the suspected etiology and the severity of symptoms, which is defined by the frequency of bowel movements per day.[14] The initial approach in mild cases is the use of antidiarrheal drugs with supportive measures including oral rehydration, electrolyte supplementation, and dietary modification as needed.[1,2,5] Any diarrhea should be considered a possible irAE. Diarrhea with abdominal cramping and fever or blood in the stool requires urgent management. When irAE is suspected, ICIs should be withheld, systemic corticosteroids initiated, and a gastroenterologist consultation considered.[13] If symptoms persist despite the use of corticosteroids, ICIs should be permanently discontinued. Surgical consultation is recommended for any grade 4 symptoms. The patient should be admitted to hospital for monitoring, IV hydration, electrolyte replacement, and high dose corticosteroid treatment.[1,2,13] If there is no improvement after 3 days of high dose steroids, infliximab should be considered.[1,2,5,13] Detailed management of diarrhea and colitis associated with ICIs is outlined in **Figure 2**.

Endocrinopathies

Endocrinopathies are less common, with around 5-20% of patients experiencing symptoms of any grade.[2,4] Typical onset is between week 12 and 24 of therapy, but may occur many months after treatment initiation.[2] The most common endocrine adverse events are thyroiditis, hypophysitis, and adrenal insufficiency.[2] Symptoms are often non-specific, such as headaches, fatigue, weakness, memory loss, impotence, amenorrhea, personality changes and visual-field impairment.[2]

Endocrinopathies are generally managed with a short course of high dose steroid treatment to reverse inflammation.[11] However, patients will likely require lifelong hormone replacement therapy as this toxicity may cause permanent sequelae.[11]

Patients often appear to have more than one endocrinopathy at once. Patients with hypothyroidism should be screened for adrenal insufficiency prior to replacement to ensure that they do not have a polyglandular auto-immune toxicity.[20] An endocrinologist should be involved and consulted as soon as endocrinopathy is suspected, with the exception of grade 1 or uncomplicated grade 2 hypothyroidism.[2]

Thyroid disorders

10-15% of patients may experience thyroiditis that partially resolves over time.[2] It may manifest as hyper or hypothyroidism and hyperthyroidism preceding a prolonged 6-10 month period of hypothyroidism.[2] Patients with thyroid disorders may be asymptomatic with detection through laboratory testing of Thyroid Stimulating Hormone (TSH) and thyroxine (T4) levels. Hypothyroidism was reported in approximately 2% of patients treated with ipilimumab, and 8% of patients treated with PD-1 inhibitors.[10] Time of onset for hypothyroidism ranged from 0.7 weeks to 19 months.[10]

Hypothyroidism is diagnosed if TSH level is increased with a low free T4 level, whereas hypophysitis presents with low TSH and low free T4.[4] The incidence of hyperthyroidism has been lower than hypothyroidism with a time of onset ranging from 24 days to 12 months.[4] Hyperthyroidism presents with low TSH and high T4; most patients later become hypothyroid due to autoimmune thyroiditis and require thyroid hormone replacement.[10] Monitoring of TSH levels prior to each dose will identify thyroid dysfunction before patients become symptomatic.[1,2]

Symptoms of hyperthyroidism can be managed with β-blockers if needed. If there are symptoms of acute thyroiditis, steroids could be considered. Hypothyroidism is managed by replacement doses of thyroid hormone.[1] Detailed management of hypo and hyperthyroidism associated with ICIs is outlined in **Figures 3 and 4**.

Hypophysitis

The incidence of hypophysitis is highest in anti-CTLA4 therapy (1%) and in combination therapy (8%). It occurs more frequently in males and usually occurs after 2-6 months of treatment.[8,9,10,11] It presents with non-specific symptoms of headache, visual impairment, fatigue, weakness, confusion, memory loss, erectile dysfunction and loss of libido, anorexia, labile moods, insomnia, temperature intolerance, subjective sensation of fever, and chills.[2,22,23]

Laboratory testing for TSH, T4, cortisol, adrenocorticotropic hormone (ACTH), luteinizing hormone (LH), follicle stimulating hormone (FSH) and growth hormone (GH) are recommended since low levels of these hormones define the diagnosis; prolactin and testosterone may also be considered.[1,2,13] Radiographic imaging (MRI) of the brain and pituitary gland may be warranted to identify lesions such as pituitary adenomas that may require intervention.[10] Acute presentations are managed by high-dose corticosteroids, which may be effective in reversing the inflammatory process and preventing long-term hormone deficiency.[1,13] Hypophysitis is managed with hormonal replacement, which is usually permanent since endogenous hormone secretion may not completely recover.[1,2] Detailed management of hypophysitis associated with ICIs is outlined in **Figure 5**.

Adrenal insufficiency

Adrenal insufficiency can be classified as primary (PAI), if the adrenal glands are impaired, or as secondary (SAI), if it is due to a failure of the hypothalamic-pituitary axis.[26] Adrenal insufficiency occurs when the adrenal cortex doesn't produce enough cortisol and patients can present with fatigue and non-specific symptoms such as hypotension, dehydration, and abnormal electrolytes that may mimic sepsis syndrome.[2,10] Monitoring of morning cortisol, ACTH, aldosterone and renin aid in diagnosis; morning cortisol < 80 nmol/L strongly suggests adrenal insufficiency.[25]

Adrenal crisis is life-threatening and requires immediate hospitalization to manage the symptoms of severe hypotension and hypovolemic shock, and to immediately rule out other causes.[1] Suspicion of adrenal crisis requires immediate administration of IV high-dose steroids with mineralocorticoid (i.e. fludrocortisone) activity soon after laboratory tests are drawn and sepsis is ruled out.[10] ICIs should be permanently discontinued. Steroid treatment is to be continued unless another cause is found and long-term steroid replacement is usually required.[13]

Suppressed adrenal function and low ACTH may be caused by exogenous steroid use. Steroid intake should be known before interpreting adrenal function, as endogenous cortisol production may be suppressed in patients taking more than 8mg of prednisone or its equivalent (e.g. 1.2 mg of dexamethasone and 30 mg of hydrocortisone) per day.[27] Detailed management of adrenal insufficiency associated with ICIs is outlined in **Figure 6**.

Diabetes

There are case reports of patients developing diabetes (usually type 1) with positive auto-antibodies.[28-30] Time to onset is 1 week to 5 months.[28] Management with insulin replacement therapy is recommended for type 1 diabetes and is usually continued long-term; corticosteroids are not recommended as they may worsen metabolic dysfunction.[28]

The management of most immune-related adverse effects requires prompt referral, assessment and treatment; patient education is critical.

Hepatic toxicities

Hepatic toxicities occur in 1-9% of patients and presents as asymptomatic elevated transaminases and, rarely, elevated bilirubin.[2,23] The usual onset is 8-12 weeks.[23] Severe hepatitis of grade 3 or higher can develop in 1-2% of cases with symptoms of fever, fatigue, abdominal pain and nausea.[31] Patients with grade 2 to 4 toxicity should be investigated to rule out other causes of hepatitis such as viral or drug-induced.[31] Cases of fulminant hepatitis, jaundice and hepatic failure have been reported in patients on ICIs.[23]

Liver function tests (LFTs) are recommended at baseline and prior to each dose.[1,5,13,31] Elevated values should prompt investigations to rule out other causes.[31] Once other causes are ruled out, systemic steroid treatment should be initiated.[1,7,23,31] Continuation, interruption, and permanent discontinuation of ICIs will depend on the relative elevation of liver enzymes to the upper limit of normal.[23] Monitoring frequency increases as the enzyme levels increase.[23] If elevation of levels persist despite steroid treatment, additional immunosuppression with mycophenolate mofetil (MMF) or tacrolimus should be considered.[1,2,5,7,13,31] Infliximab has been reported to cause hepatotoxicity in other disease states.[32] This has not been tested in patients with immune related hepatotoxicity secondary to the use of immune checkpoint inhibitors. In the case of severe ICI hepatotoxicity, the decision to use infliximab should be made after careful consideration of risk and benefit, and discussion with the patient. Highly refractory cases with rapid clinical decompensation may benefit from addition of anti-thymocyte globulin.[1,4,5,23] LFT monitoring should continue even after completion of immunosuppression and apparent resolution, as rebound elevation has been reported.[1,2,13] Detailed management of hepatic toxicities associated with ICIs is outlined in **Figure 7**.

With combination treatment, immune-related adverse effects are more common and severe, develop earlier and may last longer than with monotherapy.

Neurotoxicities

Neurotoxicities occur in less than 5% of patients and typically occurs at 1-6 weeks after initiation of treatment.[1,33] Both the peripheral and central nervous systems may be affected.1 Peripheral neuropathies may occur with sensory neuropathies, and rarely Guillain-Barré-like or myasthenia-like syndrome.[1,22,23,33] Cases of lymphocytic meningitis have been reported with iplimumab. Findings such as a high lymphocyte count in CSF supports the diagnosis.[1,23]

If the patient is asymptomatic, or presents with only mild symptoms ICI treatment may be continued.[9,22,23] Onset of moderate symptoms should prompt temporary discontinuation of ICIs, initiation of systemic steroids, and close monitoring for progression, until the nature of the adverse event is understood.[9,22,23] Any CNS or severe motor or sensory neuropathy requires permanent discontinuation of therapy.[1,9,13,22] If there is no response to initial corticosteroid treatment, the neurotoxicity is considered to be life-threatening.[9,22] When this happens, the steroid dose should be increased and neurology consulted.[1,9,22] It is important to note that treatment with steroids is not universally effective and some patients may require IV immunoglobulin, or other immunosuppressive agents. Some patients may benefit from supportive medications, such as pyridostigmine bromide and neurology should be consulted for guidance.[1] Detailed management of neurotoxicities associated with ICIs is outlined in **Figure 8**.

Pneumonitis

Pneumonitis is more likely to occur with patients on anti-PD1 immunotherapy than patients on anti-CTLA4; however, other etiologies should be excluded.[1,31,34] Less than 5% of patients on monotherapy will experience immunotherapy-related pneumonitis of any grade and 1-2% may experience pneumonitis of grade 3 or higher.[34,35] The overall incidence increases to 10% when on combination therapy.[4] The median time of onset is 19 weeks (range 0.3-84 weeks) for pembrolizumab, 9 weeks (range 4-26 weeks) for nivolumab and 11 weeks when combination therapy is utilized.[7] Patients may present with new or worsening symptoms of shortness of breath, cough, chest pain and hypoxia.[1,31,34] CT imaging may show reticular infiltrates with ground glass opacities and consolidation in patients on anti-PD1 immunotherapy, while some patients on anti-CTL4 immunotherapy may have a pattern of non-specific pneumonitis or have sarcoid-like granulomas and/or cryptogenic organizing pneumonia.[34] Symptoms may appear anytime but are more likely to occur several months after the initiation of treatment.[1]

Diagnosis based solely on radiographic changes requires close surveillance without the need for dose delay. [23,34] If the patient is symptomatic and other diagnoses have been ruled out, ICIs should be discontinued until the patient is asymptomatic.[9, 23,31,34,35] Symptomatic patients are monitored daily, initiated on systemic steroid treatment and considered for hospitalization.[9,13, 23,31,34,35] Persisting or worsening symptoms require permanent discontinuation of therapy and immediate hospitalization for urgent interventions like endotracheal intubation or tracheostomy and administration of high doses of steroids.[1,2, 9, 23,31,34,35] If symptoms worsen or do not improve after 48 hours, additional immunosuppression with infliximab, mycophenolate mofetil, cyclophosphamide, or IV immunoglobulin should be considered.[1,2,9, 23,31,34,35]

Antibiotics should also be considered if there is suspicion of concurrent infection and if patients are expected to receive more than 4 weeks of immunosuppression as prophylaxis against opportunistic infections (especially pneumocystis pneumonia).[9,23,31,34] Detailed management of pneumonitis associated with ICIs is outlined in **Figure 9**.

When using corticosteroids to treat immune-related adverse effects, the dose must be tapered over at least 2-4 weeks (depending on the doses used), and long-term use may require prophylaxis for opportunistic infections.

Renal toxicities

Renal toxicities affect less than 5% of patients and often appear at 13 weeks of treatment, but can appear as early as 6 weeks to as late as 30 weeks.[7,9,23,36] Renal failure may initially present with increased serum creatinine without any clinical features; however, the patient may progress to anuria, oliguria, edema and electrolyte disorders.[7,23,36]

Management is primarily dependent on the level of serum creatinine (SCr) and proteinuria since clinical symptoms usually present later. Monitoring for elevated SCr should be done prior to initiating and periodically during treatment.[10] Interruption or permanent discontinuation of therapy and frequency of monitoring is dependent on the levels of SCr. Treatment includes the use of systemic steroids and supportive treatments such as monitoring for fluid electrolyte imbalances, hydration, and discontinuation of nephrotoxic drugs.[9,23] In the absence of response or worsening of symptoms, nephrology consult, biopsy, and additional immunosuppressive regimens should be considered.[7,9,10] Detailed management of renal toxicities associated with ICIs is outlined in **Figure 10**.

Ocular toxicities

Ocular toxicities occur in less than 1% of patients on ipilimumab and rarely in patients on PD-1 inhibitors. These may involve uveitis and, less commonly, episcleritis and conjunctivitis.[2,5,11,13,23] Patients with ocular symptoms should be evaluated by an ophthalmologist and can be treated with ophthalmic corticosteroids in cases involving mild symptoms with no vision changes.[2,5,11,13,23] In more serious cases that are refractory to topical steroids or cases involving vision changes, ICIs should be discontinued and the patient should be started on oral prednisone at 1-2mg/kg or its IV equivalent.[23]

Hematological

Hematological adverse effects have been reported in patients on ICIs. Presentation can range from mild asymptomatic cytopenias to more serious events including neutropenia, red cell aplasia and acquired hemophilia.[1,5,13] Patients should be treated with systemic corticosteroids (e.g. prednisone 1mg/kg/day), ICIs should be discontinued and blood transfusions administered as required.[1] If the patient does not respond to steroids then IV immunoglobulin with or without immunosuppressants may be used.[1]

Inflammatory arthritis

Immune-related inflammatory arthritis is estimated to occur in 1-7% of patients on immune checkpoint inhibitor therapy.[37,38] Clinical presentation may resemble rheumatoid arthritis, reactive arthritis, or seronegative spondyloarthritis.[37] Symptoms may include joint pain, stiffness (primarily in the morning or after being sedentary), erythema, warmth, swelling in the upper and lower extremities, and symmetrical swelling of the proximal interphalangeal joints, metacarpophalangeal joints, and/or wrists.[37,38] These symptoms may persist more than a year after discontinuing ICI therapy.[37] Early identification and control of inflammatory arthritis is critical to prevent progression to erosive joint damage and referral to rheumatology should always be considered.[37,38]

Typical treatment options for immune-related inflammatory arthritis include NSAIDs (e.g. naproxen 500 mg twice a day), low dose corticosteroids (e.g. prednisone 10-20 mg daily x 4-6 weeks), holding ICIs, high dose corticosteroids (e.g. prednisone 1mg/kg/day or equivalent), or additional immunosuppression (e.g. methotrexate) depending on the severity of the symptoms.[37] Intra-articular steroids can be considered if only 1-2 joints are affected and NSAIDs or low dose corticosteroids are not effective and the patient is not at high risk for joint infection.[37]

Oral toxicities

Oral toxicities such as mucositis, gingivitis and sicca syndrome are more common in anti-PD-1 agents than anti-CTLA-4 agents. The incidence rate of oral toxicities at any grade is 6.5%.[39] These toxicities can be managed by supportive care including oral rinses with topical steroids, viscous lidocaine and good oral hygiene.[40]

Cardiotoxicity

Immune-related cardiotoxicity is very rare (< 1%) and may include myocarditis, pericarditis, arrhythmias, cardiomyopathy and left ventricular dysfunction.[41-43] Early cardiologist referral is recommended along with high-dose corticosteroids (e.g. prednisone 2mg/kg/day).[42,43] If symptoms do not respond quickly, consider other immunosuppressants such as infliximab and MMF.[4]

Key Points in the Management of Immune-Related Adverse Effects

If no other cause can be identified (such as infection), any new symptom should be considered immune-related and prompt treatment initiated.

- Immune-related adverse effects (irAEs) are different in their presentation, onset and duration compared to conventional chemotherapy. Patient and provider education is essential.
- Initial irAE presentation can occur months after completion of treatment and affect multiple organs.
- Organ-specific system-based toxicity management is recommended.
- In general, immune checkpoint inhibitor (ICI) therapy should continue with close monitoring for Grade 1 irAEs.
- For most Grade 2 toxicities, ICI therapy should be held and corticosteroids initiated.
- For most grade 3 irAEs, ICI therapy should be held and high-dose corticosteroids initiated.
- Corticosteroids should be tapered (over at least 2-4 weeks, depending on the dose) once irAEs resolve to Grade 1 or less. Long-term use may require prophylaxis for opportunistic infections.
- Other immunosuppressant agents may be required if irAEs do not improve with corticosteroids.
- When irAEs resolve to Grade 1 or less, re-challenging with the ICI may be considered, if benefits outweigh risks.
- For most Grade 4 irAEs, ICI therapy should be permanently discontinued.

General Considerations for Patients on ICIs

High dose corticosteroids/ other immunosuppressants

Patients on high dose corticosteroids or other immunosuppressants may benefit from anti-microbial prophylaxis against opportunistic infections. Prophylaxis against Pneumocystis jirovecii pneumonia (PCP) should be initiated in patients treated with 20 mg or more per day of prednisone or equivalent for 4 weeks or more.[1,3,5,6,10,23,44]

The recommended prophylactic therapy for PCP is sulfamethoxazole/trimethoprim. Dosing schedules vary depending on institutional guidelines and clinical judgement; example dosing schedules include sulfamethoxazole/trimethoprim single strength 80/400mg once daily or double strength (DS) 160mg/800mg q12h 3 x weekly.[6,45,46] Consider other options such as pentamidine in patients with sulfa allergy.[6] If stronger immunosuppressants are required, the patient should be investigated for viral hepatitis, latent tuberculosis and be initiated on appropriate prophylaxis if needed.[6,13,44]

Autoimmune disorders

Patients with autoimmune disorders may still receive ICI therapy.[47] 50% of patients will experience either an exacerbation of prior symptoms of their autoimmune disorder or an irAE. These exacerbations are treatable with low dose corticosteroids, with some patients requiring high dose corticosteroids.[47] Events can occur at any time but most occur between 2 to 6 weeks after the initiation of ICIs.[47] The frequency of other irAEs is similar to patients without immune disorders.[47] Patients with autoimmune disorders should continue with ICIs, careful monitoring and receive treatment for their symptoms when they arise.[47]

Vaccines

Given the current lack of evidence, patients on immune checkpoint inhibitors should avoid live vaccines. Literature around the use of inactivated vaccines is evolving. One small study reported an increased risk of irAEs with the inactivated influenza vaccine, whereas another study showed no difference.[48,49] All vaccinations should be considered only after careful assessment of the risks vs. benefits.

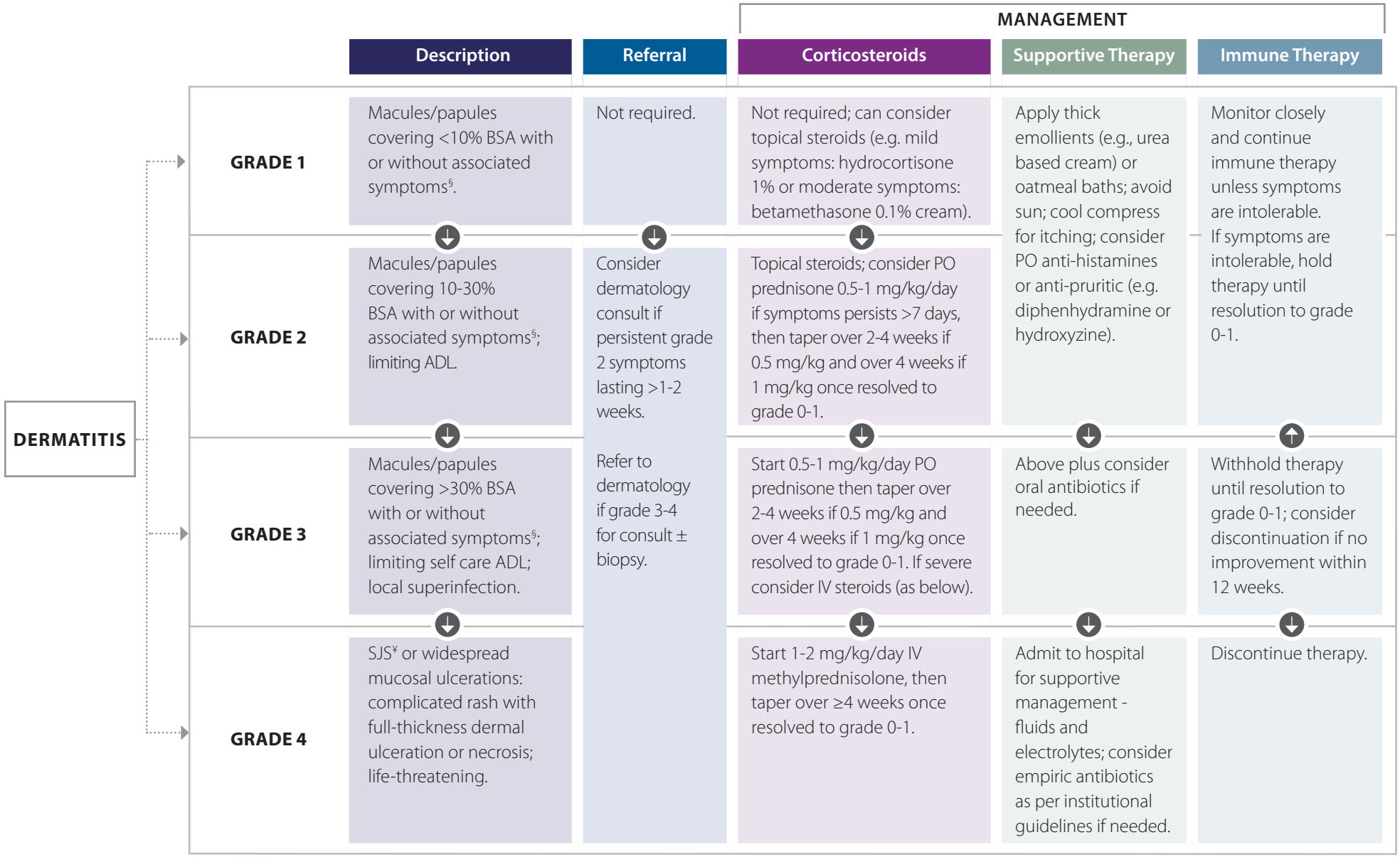
Figures:

Immune checkpoint inhibitor toxicity management algorithms

FIGURE 1

Management of Immune-Related Dermatologic Toxicities[1,2,4,10,13,14]

Background: Skin toxicities related to immune therapy typically presents as erythematous, reticular, and maculopapular rash and are often located across the trunk and extremities. The median time to onset is 3 to 6 weeks (ranges up to 17 weeks for ipilimumab and nivolumab). Pruritus, sometimes severe, may occur in the absence of a frank rash. Rashes are usually mild (grade 1-2) and can be managed symptomatically. Severe rashes (grade 4), such as bullous pemphigoid, Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrosis (TEN), are reported in <5% of patients. Any signs of desquamation at any grade should be considered a medical emergency and treated as grade 4.



§ As per CTCAE version 4.0 = pruritus, burning, tightness or equivalent

¥ Symptoms indicative of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN): macules rapidly spread and coalesce, leading to epidermal blistering, necrosis, and sloughing.

FIGURE 2

Management of Immune-Related Diarrhea/Colitis[1,4,5,10,13,14,17-19]

Background: It is important to rule out other etiologies that may be responsible for diarrhea, such as *C.difficile* infections. Severe diarrhea has been observed in patients treated with immune therapy. The median time to onset is 6 to 8 weeks for ipilimumab and nivolumab, and 3.4 months for pembrolizumab. Diarrhea/colitis appears to be less frequent with PD-1 blockade than with CTLA-4 blockade.

DIARRHEA/ COLITIS

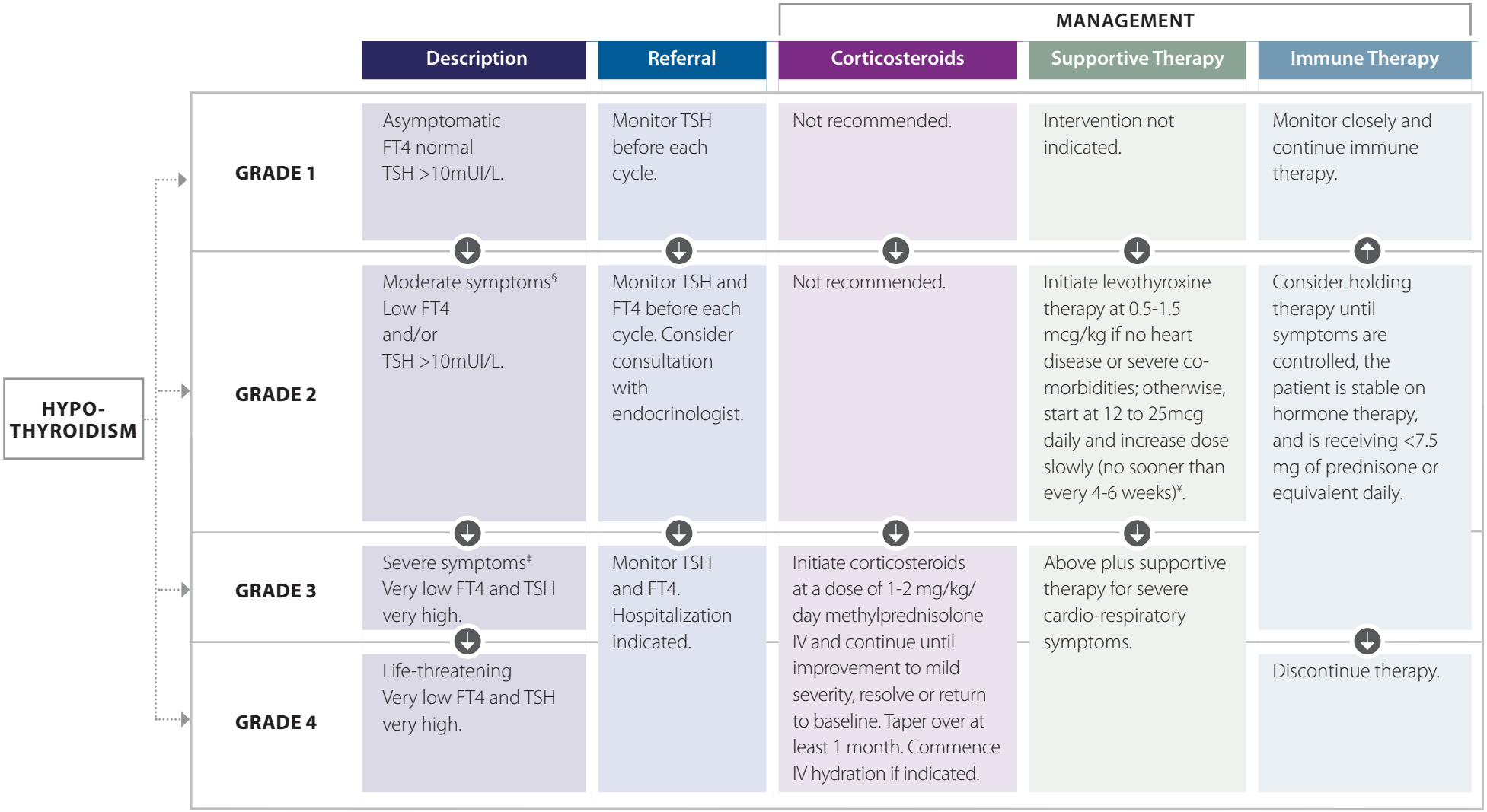
	Description	Referral	MANAGEMENT (First rule out infectious causes) Corticosteroids	Supportive Therapy	Immune Therapy
GRADE 1	<4 stools/day above baseline.	Not required.	Not required.	Initiate loperamide£ therapy; maintain oral hydration; consider electrolyte supplementation and dietary modifications.ϕ	Monitor closely and continue immune therapy.
GRADE 2	4-6 stools/day above baseline; abdominal pain, mucus or blood in stool.	Refer to a gastroenterologist for flexible sigmoidoscopy or colonoscopy for persistent grade 2 diarrhea (especially if diagnosis is in question) or any grade 3-4 diarrhea. If any chance of perforation avoid colonoscopy and suggest surgical consult.	Consider starting steroids right away (do not need to wait for consult) or if no improvement after 24 hours of loperamide. Start 0.5-1 mg/kg/day PO prednisone† until resolution to grade 0-1. Then taper over 2-4 weeks if 0.5 mg/kg and over 4 weeks if 1 mg/kg. If no improvement in 72 hours, treat as grade 3-4.	Start loperamide£ and monitor after 24 hours; continue if symptoms improved. Consider prednisone if symptoms worsen or no resolution; give oral/IV hydration; consider electrolyte supplementation and dietary modifications.ϕ	Withhold therapy until grade 0-1 and on prednisone <7.5 mg/day (CTLA-4) or <10 mg/day (PD-1). Consider discontinuation if no improvement within 12 weeks or inability to reduce steroids.
GRADE 3	≥7 stools/day above baseline; incontinence, need for hospitalization for IV fluids ≥24hrs.		Start 1-2 mg/kg/day IV methylprednisolone until improvement, then slow taper over ≥4 weeks. If no response after 3 days, give infliximab 5 mg/kg IV once every 2 weeks* (use with caution in grade 4 due to risk of perforation and avoid if contraindicated).	Admit to hospital and initiate IV hydration. Consider empiric antibiotics as per institutional guidelines for patients who present with fever/leukocytosis. Use opioid analgesics with caution due to risk of narcotic bowel.	Permanently discontinue therapy.
GRADE 4	Grade 3 plus fever, or peritoneal signs consistent with bowel perforation, or ileus; life-threatening.	Suggest surgical consult.			

£ loperamide 4 mg followed by 2 mg q4h or after every loose BM until diarrhea-free for 12hrs (max 16 mg/day)
† or equivalent
ϕ Refer to CCO Diarrhea Guidelines: https://www.cancercareontario.ca/en/symptom-management/3151
* If infliximab is contraindicated (possibility of perforation, sepsis, TB, NYHA 3/4 CHF), consider mycophenolate mofetil or other immunosuppressive agents

FIGURE 3

Management of Immune-Related Hypothyroidism[4,6,10,14,21]

Background: Around 5-10% of patients receiving CLTA-4 and anti-PD-1/PD-L1 antibodies are likely to develop an endocrine adverse event of any grade. Hypothyroidism was reported in approximately 2% of patients treated with ipilimumab, and 8.3% of patients treated with PD-1 inhibitors. Time of onset for hypothyroidism ranged from 0.7 weeks to 19 months. Hypothyroidism is diagnosed if TSH level is increased with a low free T4 level. When thyroid replacement is given, dose adjustments should occur no sooner than 4-6 weeks. An endocrinologist should be consulted with the exception of grade 1 or uncomplicated grade 2 hypothyroidism.



§ Fatigue, constipation, weight gain, loss of appetite, dry skin, eyelid edema, puffy face, hair loss

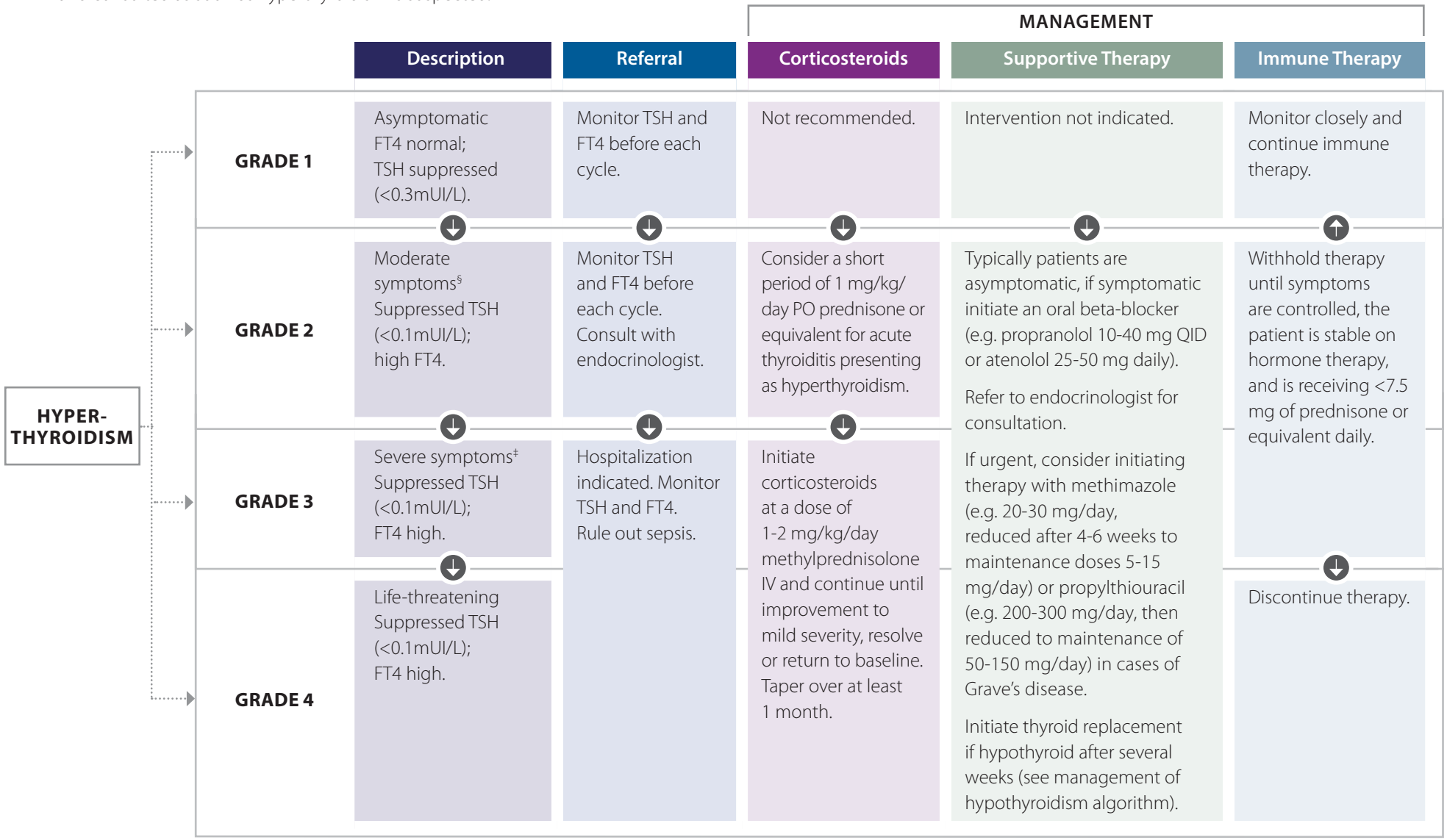
‡ Bradycardia, hypotension, pericardial effusion, depression, hypoventilation, stupor, lethargy to myxedema coma

¥ If patient has both adrenal insufficiency and hypothyroidism, start corticosteroid for 2-3 days before levothyroxine

FIGURE 4

Management of Immune-Related Hyperthyroidism[6,10,14,21]

Background: Around 5-10% of patients receiving CLTA-4 and anti-PD-1/PD-L1 antibodies are likely to develop an endocrine adverse event of any grade. Patients with thyroid disorders may be asymptomatic. Detection of hyperthyroidism is through laboratory testing of TSH and T4 levels. The incidence of hyperthyroidism has been lower than hypothyroidism with a time of onset ranging from 24 days to 12 months. Hyperthyroidism is characterized by high or normal levels of free T4 in the body and presents with low TSH. Most patients later become hypothyroid due to autoimmune thyroiditis and require thyroid hormone replacement. An endocrinologist should be involved and consulted as soon as hyperthyroidism is suspected.



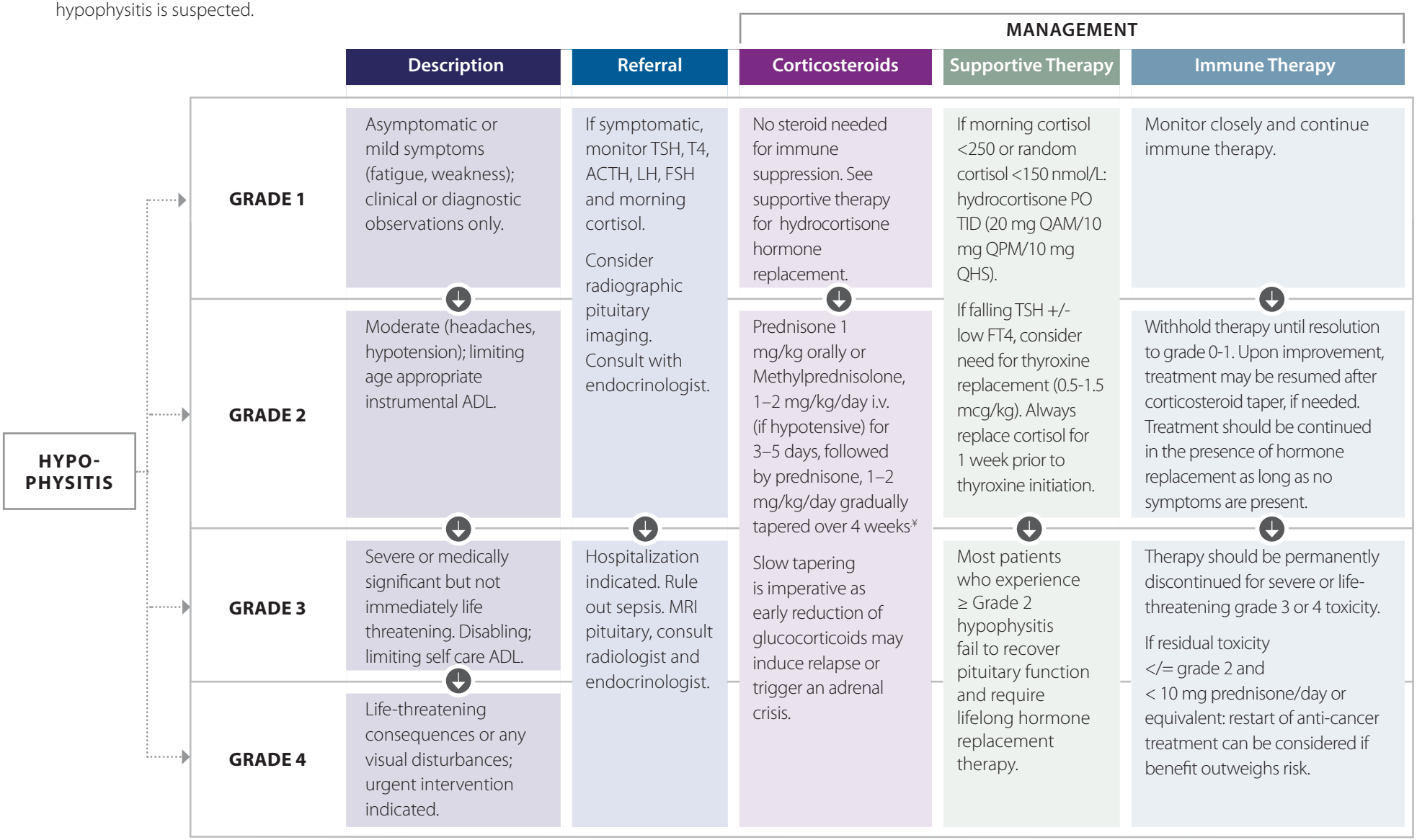
§ Weight loss, increased appetite, anxiety and irritability, muscle weakness, menstrual irregularities, fatigue, tachycardia

‡ Arrhythmia, atrial fibrillation, tremor, sweating, insomnia, diarrhea

FIGURE 5

Management of Immune-Related Hypophysitis[2,4,10,13,14,17,23,24,25]

Background: The incidence of hypophysitis is highest in anti-CTLA4 therapy (1%) and in combination therapy (8%). It occurs more frequently in males and usually occurs after 2-6 months of treatment. Hypophysitis can remain undetected since the symptoms might be vague[§] Laboratory testing of morning cortisol, adrenocorticotropic hormone (ACTH), luteinizing hormone (LH), follicle stimulating hormone (FSH) and growth hormone (GH) define the diagnosis. Hypophysitis presents with low TSH and low free T4. Radiographic imaging (MRI) of the brain and pituitary gland may be warranted to identify lesions such as pituitary adenomas that may require intervention. Hormone replacement should be initiated according to hormone dysfunction and is usually long-term. An endocrinologist should be involved and consulted as soon as hypophysitis is suspected.



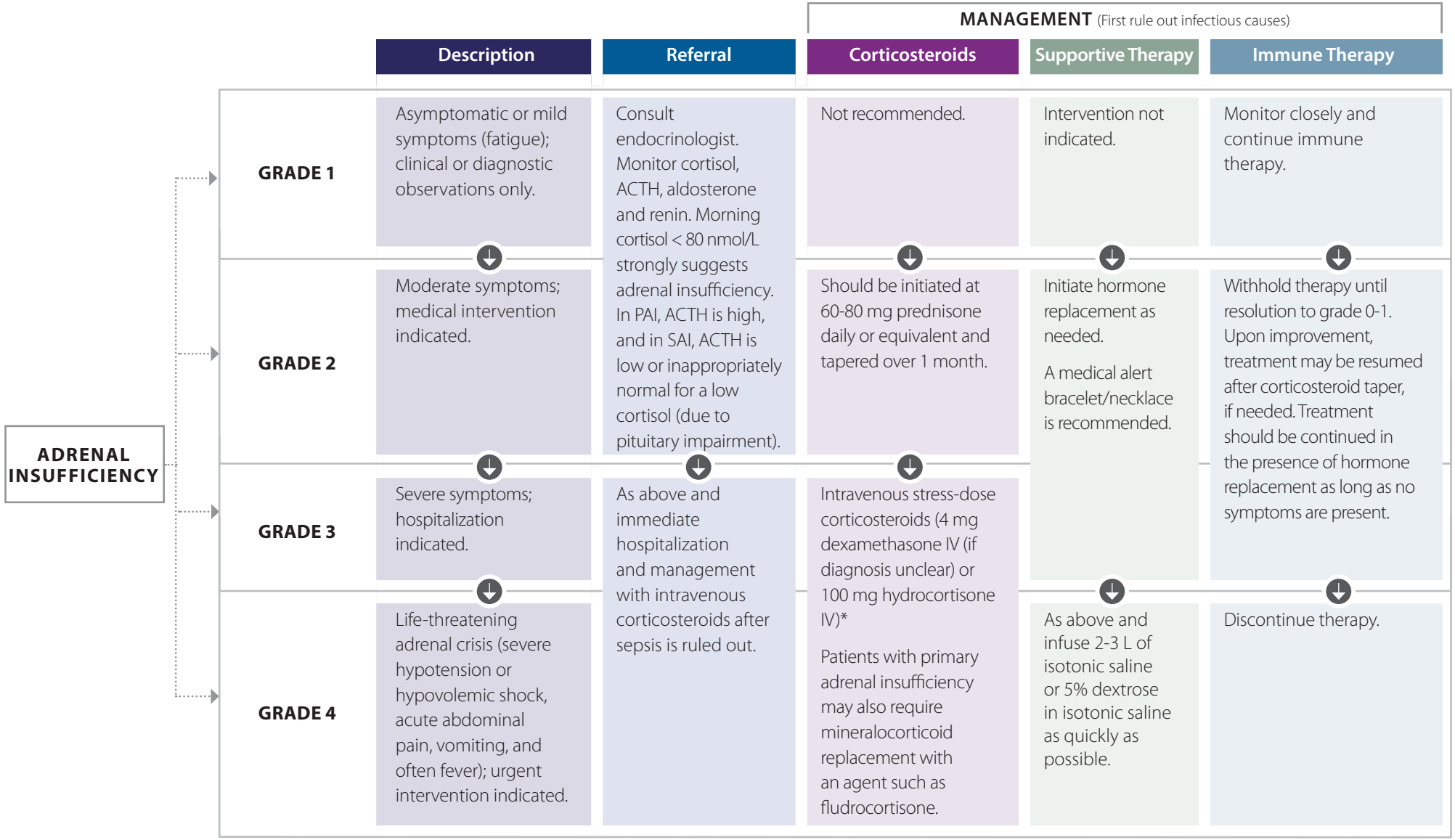
§ Nonspecific symptoms such as headache, visual impairment, fatigue, weakness, confusion, memory loss, erectile dysfunction and loss of libido, anorexia, labile moods, insomnia, temperature intolerance, subjective sensation of fever, and chills.

¥ Alternatively dexamethasone, 4 mg every 6 hours for 1 week, gradually tapered to 0.5 mg/d, with substitution to replacement doses of hydrocortisone.

FIGURE 6

Management of Immune-Related Adrenal Insufficiency[2,4,10,13,14,17,23,24,25]

Background: Adrenal insufficiency can be classified as primary (PAI) if the adrenal glands are impaired or as secondary (SAI) if it is due to a failure of the hypothalamic-pituitary axis. Adrenal insufficiency occurs when the adrenal cortex does not produce enough cortisol (and in some cases aldosterone) and is usually characterized by hypotension, dehydration, and abnormal electrolytes, such as hyponatremia and hyperkalemia, that may mimic sepsis syndrome. Adrenal insufficiency is rare and has been reported in 0.7% of patients treated in randomized clinical trials. Adrenal insufficiency requires immediate intravenous corticosteroids after sepsis is ruled out, followed by an oral corticosteroid taper. Long-term steroid replacement is usually required. An endocrinologist should be involved and consulted as soon as adrenal insufficiency is suspected.

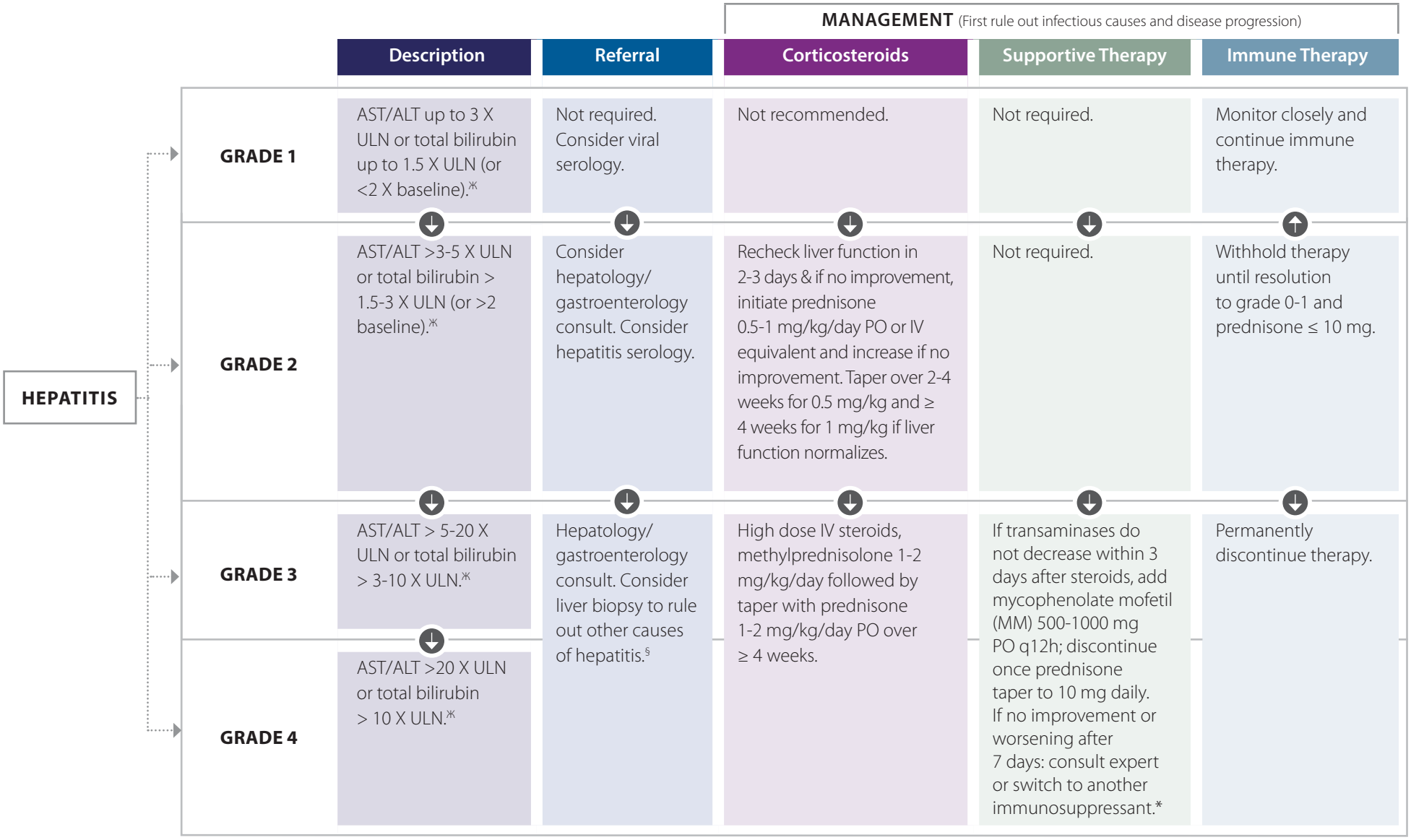


* Hydrocortisone is recommended if confirmed PAI. Continue dexamethasone 4 mg every 12 hours and hydrocortisone 200 mg per 24 hours (via continuous infusion or q6h bolus). Taper to maintenance doses over 2 weeks post-discharge.

FIGURE 7

Management of Immune-Related Hepatic Toxicities[1,4,5,7,8,11,13,14,23,31]

Background: Hepatotoxicity related to immune-therapy typically presents as elevated LFTs mainly AST, ALT, GGT and rarely bilirubin. The patient is usually asymptomatic and onset is variable with average 8-12 weeks after start of therapy. Rarely, patients present with fever, fatigue, nausea and abdominal pain. Monitoring LFTs are recommended at baseline and prior to each dose. Hepatic adverse events are usually grade 1-2 and occur in approximately 1-6% of patients on PD-1 inhibitors and more frequently in patients on CTLA-4 inhibitors but still <10%.



§ Hepatitis A, C, CMV

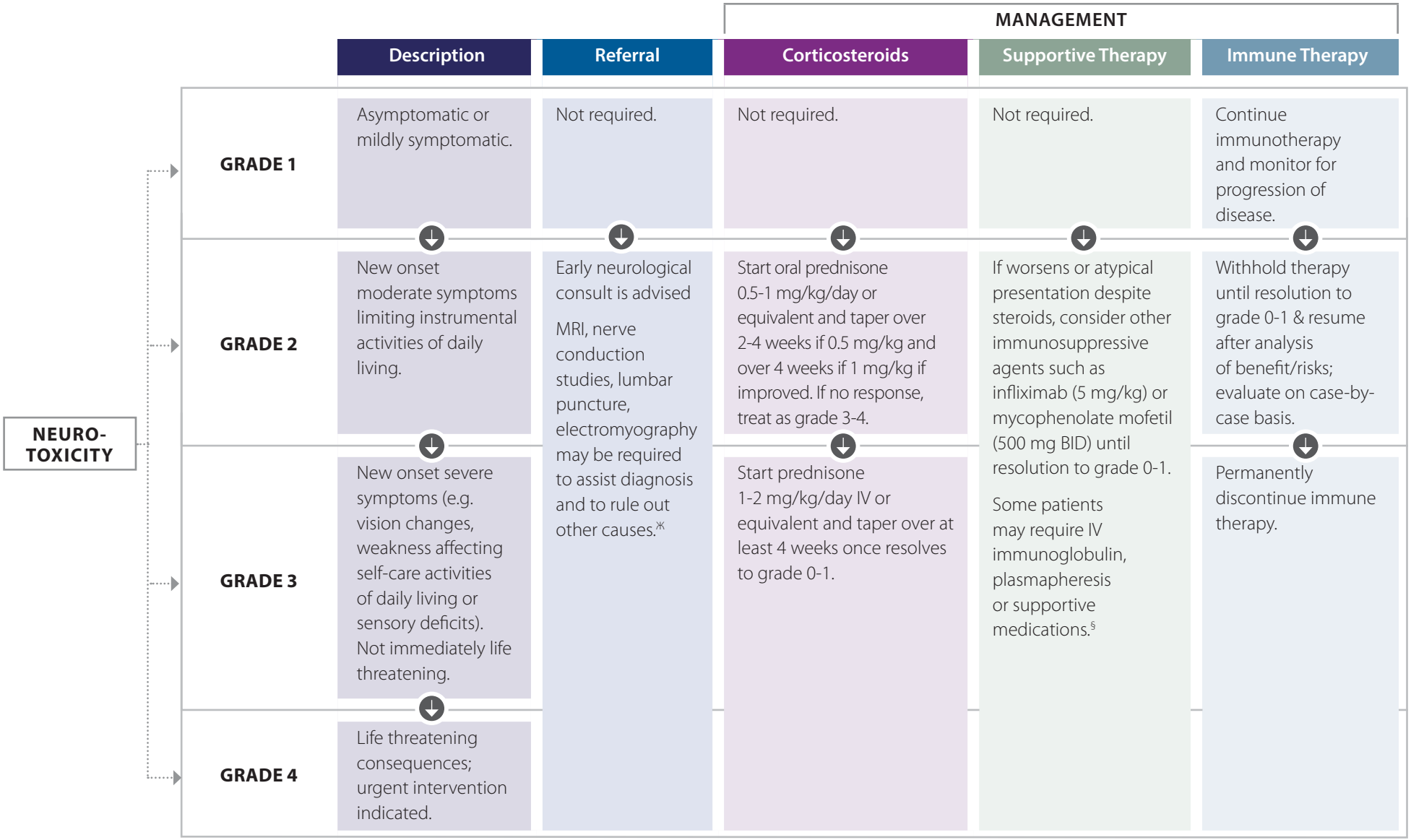
* Tacrolimus 0.10-0.15 mg/kg/day; in the case of severe hepatotoxicity, the decision to use infliximab should be made after careful consideration of risk and benefit, and discussion with the patient.

⁂ For patients being treated with ICIs for hepatocellular carcinoma, these values may differ. Refer to the ICI product monograph.

FIGURE 8

Management of Immune-Related Neurotoxicities[1,9,13,14,22,23,33]

Background: Neurologic toxicities related to immune therapy are potentially antibody-mediated events that can range from mild paresthesia to severe such as Guillain-Barré syndrome, severe motor neuropathy, myasthenia gravis (which can be life threatening but occurs extremely rarely at <1%). Neurotoxicity can be sensory, motor and/or CNS which encompasses enteric neuropathy, inflammatory myopathy, lymphocytic meningitis, cerebral vasculitis and optic neuritis. Immune-related neurologic toxicity typically occurs at 1-6 weeks after initiation of treatment.



§ Pyridostigmine bromide for myasthenia gravis disease

⁂ Infectious causes, disease progression etc.

FIGURE 9

Management of Immune-Related Pneumonitis[1,7,9,14,23,31,34]

Background: Pneumonitis is a non-infectious lung inflammation with interstitial and alveolar infiltrates. Although pneumonitis is rare (<5%) it can be life threatening; fortunately, the incidence of grade 3 or 4 toxicity is low (<1%) for both CTLA-4 and PD-1 blocking antibodies. Clinical presentation includes dry, unproductive cough, tachypnea, dyspnea, tachycardia, cyanosis, and fatigue. Oxygen saturation may fall with progression, especially after exercise. Chest imaging typically shows ground glass opacities or patchy nodular infiltrates, particularly in lower lobes. The median time of onset of pneumonitis is 19 weeks (range 0.3-84 weeks) for pembrolizumab, 9 weeks (range 4-26 weeks) for nivolumab and 11 weeks when on combination therapy.

PNEUMONITIS

MANAGEMENT (First rule out infectious causes)

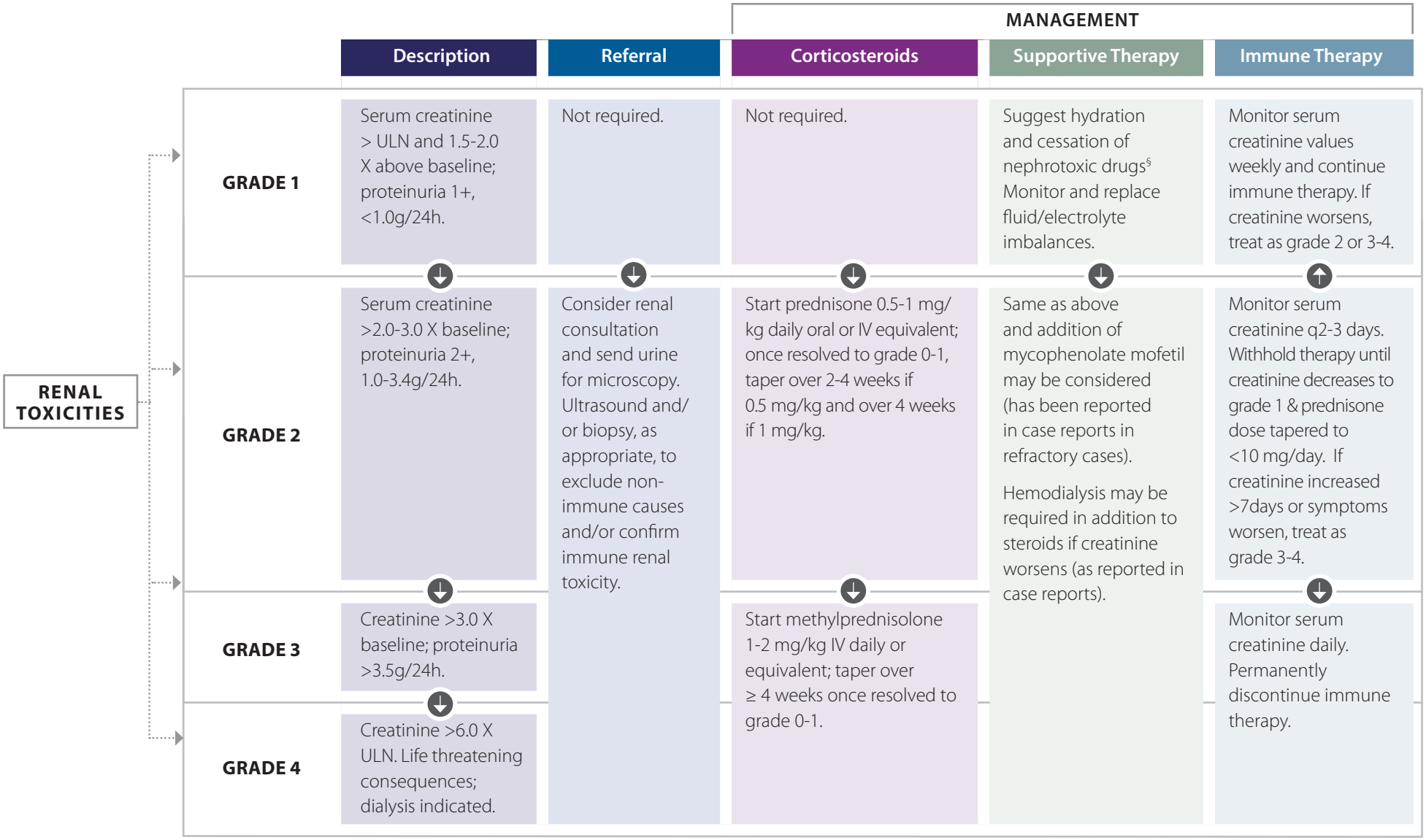
	Description	Referral	Corticosteroids	Supportive Therapy	Immune Therapy
GRADE 1	Asymptomatic; diagnostic radiological observations only; no intervention needed.	Monitor oxygen saturation and chest x-ray or CT every cycle and consider pulmonary and infectious disease consults.	Consider 1 mg/kg/day PO prednisone or 1 mg/kg/day IV methylprednisolone.	Not required.	If patient is on steroids, consider withholding treatment until resolution.
GRADE 2	Symptomatic; medical intervention indicated; limiting instrumental ADL.	Pulmonary and infectious disease consults.	Start 1-2 mg/kg/day PO prednisone or IV equivalent, taper over ≥4 weeks. If no improvement after 48 to 72 hours or worsening, treat as grade 3-4.	Consider hospitalization for daily monitoring of symptoms and re-imaging every 1-3 days. Start empiric antibiotics if suspicious for infection.	Withhold therapy until resolution to grade 0-1 without complications & prednisone dose tapered to <10 mg/day. Discontinue immune therapy if toxicity recurs.
GRADE 3	Severe symptoms; limiting self care ADL; oxygen indicated.	Pulmonary and infectious disease consults. Consider bronchoscopy & lung biopsy to investigate for pulmonary infection.	Start 2-4 mg/kg/day methylprednisolone IV then taper over ≥6 weeks; if no improvement after 48 hours or worsening, additional immunosuppression such infliximab 5 mg/kg IV once q2weeks can be administered (avoid if contraindicated*).	Admit to hospital and start prophylactic antibiotics for opportunistic infections. Oxygen and ventilation support if necessary.	Permanently discontinue therapy.
GRADE 4	Life-threatening respiratory compromise; urgent intervention indicated (e.g. intubation and ventilation).				

* If infliximab is contraindicated (possibility of perforation, sepsis, TB, NYHA 3/4 CHF), consider mycophenolate mofetil (500-1000 mg BID) or other immunosuppressive agents

FIGURE 10

Management of Immune-Related Renal Toxicities[4,7,9,10,14,23,36]

Background: Renal failure related to immune checkpoint inhibitors occurs in <5% of patients. It typically presents without any clinical features at the beginning, but rising creatinine values can be detected. With progression, symptoms such as oliguria, edema, anuria and electrolyte abnormalities can occur (e.g. hyperkalemia). Median onset of immune-related events ranges from 6 to 10.5 weeks and may present months after discontinuation of therapy.



§ i.e. aminoglycosides, contrast agent etc.

Acknowledgements

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This clinical practice guideline was developed by a multidisciplinary working group of oncology clinicians with experience in the use of immune checkpoint inhibitors. The recommendations are based on best available evidence, current practice in Ontario, guidance from clinical experts, and working group consensus.

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