IN PURSUIT OF *YOUR CURE.*™

Toxicities in Immunotherapy

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SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

NCI Cancer Center
A Cancer Center Designated by the National Cancer Institute

Objectives

1. Recognize benefits of immune checkpoint inhibitors
2. Monitor some Immune-Related Adverse Events
3. Appropriately recognize and treat irAE

Immunotherapy has revolutionized the treatment of many different types of cancers; such as melanoma, non-Hodgkin lymphoma, lung, renal, bladder, breast, head and neck.

- Target cytotoxic T-Lymphocytes associated with antigen-4 (CTLA-4)
- Programmed cell death -1 (PD-1), and PD ligand 1(PD-L1) work by preventing the receptors and ligands from binding to each other, thereby disrupting signaling so that T cells can recognize and attack cancer cells
- They are currently the standard of care in several solid organ and hematologic malignancies.
- The use of ICP's is rising.

Immunotherapy by the Numbers

2011
First immunotherapy for cancer approved in 2011.

70
More than **70 immunotherapy drugs are in the clinical pipeline.**

2017
FDA has approved four immunotherapy checkpoint inhibitors as of early 2017.

25
There is so much pharmaceutical R&D that **cancer immunotherapy has its own stock index of 25 companies worth $100 million or more.**

$21.36
It is predicted to be USD 75.36 billion by 2028 from **USD 21.36 billion in 2023.**

15-20%
15-20% of patients achieve durable results with immunotherapy.

1,000
More than 1,000 immunotherapy clinical trials are underway across the country.

https://www.hopkinsmedicine.org/inhealth/about-us/immunotherapy-precision-medicine-action-policy-brief

CHECKPOINT INHIBITORS (CPI) MAY PROVOKE UNPREDICTABLE, POTENTIALLY SEVERE AND POSSIBLY PERMANENT IMMUNE RELATED SIDE EFFECTS

- Pre-existing active autoimmune diseases requiring immune suppression, generally are considered contraindication for treatment with CPI's (clinical trials)
- Generally, ICPi therapy should be continued with close monitoring for grade 1 toxicities, except for some neurologic, hematologic, and cardiac toxicities
- ICPi therapy may be suspended for most grade 2 toxicities, with consideration of resuming when symptoms revert ≤ grade 1.
- Corticosteroids may be administered. Grade 3 toxicities generally warrant suspension of ICPis and the initiation of high-dose corticosteroids. Corticosteroids should be tapered over the course of at least 4-6 weeks. Some refractory cases may require other immunosuppressive therapy

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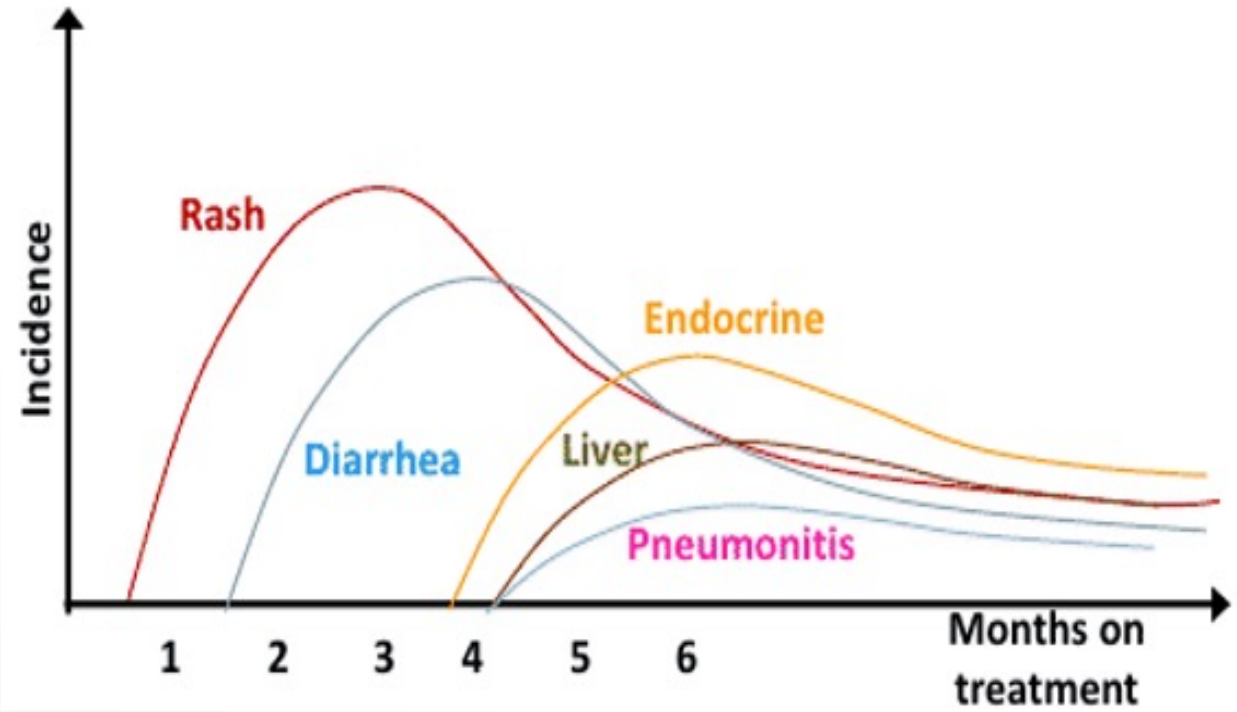
EXAMPLES OF IF IMMUNE CHECKPOINT INHIBITORS

CTLA-4	Ipilimumab
PD1	Pembrolizumab, Nivolumab
PDL1	Atezolizumab, Durvalumab, Avelumab

Onset and Duration of irAEs

- irAEs may occur at any time during treatment.
  - Time to irAE onset can range from within the first few weeks, months, to up to a year after treatment initiation.
  - Most irAEs will occur during the first few doses
  - The pattern of onset may vary by organ system.
- Risk of irAEs does not appear to be dose-dependent for anti-PD-1 agents.
- irAEs from immunotherapy can have a delayed onset and prolonged duration, in part due to PK/PD differences in comparison with chemo.
- Moreover, the relationship between irAEs and dose/exposure remains to be fully established.



- *Understanding immunotherapy side effects - NCCN*. National Comprehensive Cancer Network. (n.d.). https://www.nccn.org/docs/default-source/patient-resources/immunotherapy_infographic.pdf?sfvrsn=f92249ca_2

Other common symptoms： fatigue, pyrexia, asthenia, alopecia,

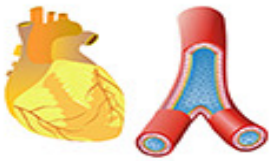
Uveitis, Myesthemia Gravis, Vasculitis, Encephalitis, myocarditis, solid organ transplant rejection, and hypophysitis Diabetes

HYPO-TIME TO ONSET .0.7 WKS-19MOS
HYPER 24DAYS -19 MOS

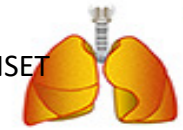
Endocrine system
Hypothyroidism
Hyperthyroidism

Cardiovascular system
Anemia
Neutropenia
Thrombocytopenia

TIME TO ONSET VARIABLE



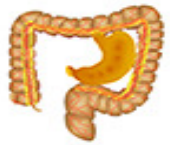
TIME TO ONSET DIFFERS BETWEEN AGENTS



Respiratory
Dyspnea
Pneumonitis

Digestive system
Colitis
Nausea
Diarrhea
Stomatitis
Decreased appetite

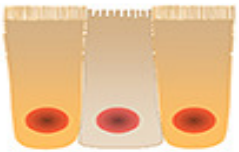
TIME TO ONSET 6-8 WEEKS



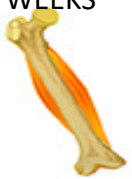
Hepatic
Hepatitis
Aspartate/Alanine aminotransferase Increase

TIME TO ONSET 3-6 WEEKS

Skin-relate
Rash
Pruritus



TIME TO ONSET VARIABLE 8-12 WEEKS



Skeletal muscle system
Myalgia
Arthralgia

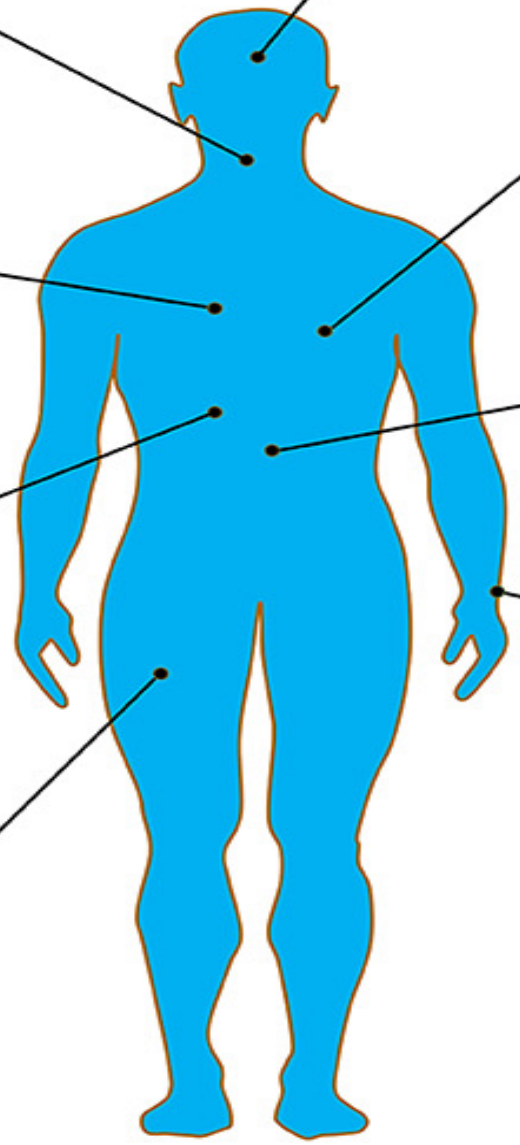
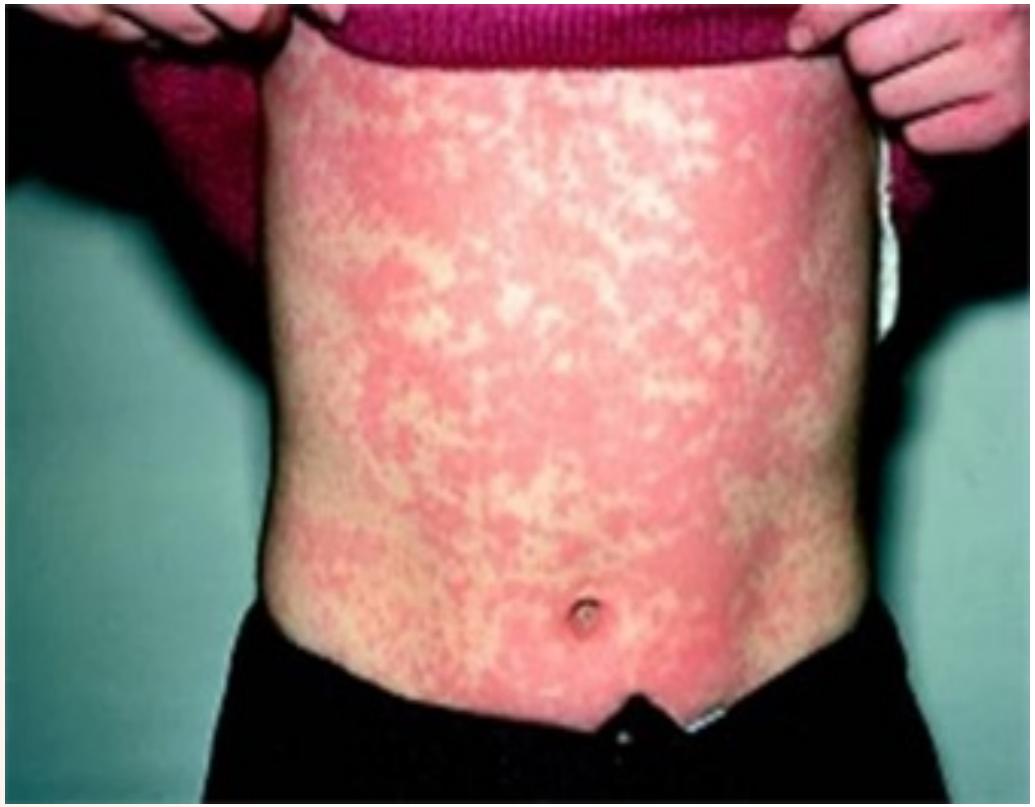


FIGURE 1

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.

		Description	Referral	MANAGEMENT: Corticosteroids	MANAGEMENT: Supportive Therapy	MANAGEMENT: Immune Therapy
DERMATITIS	GRADE 1	Macules/papules covering <10% BSA with or without associated symptoms[5].	Not required.	Not required; can consider topical steroids (e.g. mild symptoms: hydrocortisone 1% or moderate symptoms: betamethasone 0.1% cream).	Apply thick emollients (e.g., urea based cream) or oatmeal baths; avoid sun; cool compress for itching; consider PO anti-histamines or anti-pruritic (e.g. diphenhydramine or hydroxyzine).	Monitor closely and continue immune therapy unless symptoms are intolerable. If symptoms are intolerable, hold therapy until resolution to grade 0-1.
	GRADE 2	Macules/papules covering 10-30% BSA with or without associated symptoms[5]; limiting ADL.	Consider dermatology consult if persistent grade 2 symptoms lasting >1-2 weeks.	Topical steroids; consider PO prednisone 0.5-1 mg/kg/day if symptoms persists >7 days, then taper over 2-4 weeks if 0.5 mg/kg and over 4 weeks if 1 mg/kg once resolved to grade 0-1.		
	GRADE 3	Macules/papules covering >30% BSA with or without associated symptoms[5]; limiting self care ADL; local superinfection.	Refer to dermatology if grade 3-4 for consult ± biopsy.	Start 0.5-1 mg/kg/day PO prednisone then taper over 2-4 weeks if 0.5 mg/kg and over 4 weeks if 1 mg/kg once resolved to grade 0-1. If severe consider IV steroids (as below).	Above plus consider oral antibiotics if needed.	Withhold therapy until resolution to grade 0-1; consider discontinuation if no improvement within 12 weeks.
	GRADE 4	SJS[¥] or widespread mucosal ulcerations: complicated rash with full-thickness dermal ulceration or necrosis; life-threatening.		Start 1-2 mg/kg/day IV methylprednisolone, then taper over ≥4 weeks once resolved to grade 0-1.	Admit to hospital for supportive management - fluids and electrolytes; consider empiric antibiotics as per institutional guidelines if needed.	Discontinue therapy.



MACULAR/PAPULAR RASH

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

		MANAGEMENT (First rule out Infectious causes)			
	Description	**Referral**	**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
ϕRefer 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.

		Description	Referral	MANAGEMENT: Corticosteroids	MANAGEMENT: Supportive Therapy	MANAGEMENT: Immune Therapy
HYPO-THYROIDISM	GRADE 1	Asymptomatic FT4 normal TSH >10mUI/L.	Monitor TSH before each cycle.	Not recommended.	Intervention not indicated.	Monitor closely and continue immune therapy.
	GRADE 2	Moderate symptoms§ Low FT4 and/or TSH >10mUI/L.	Monitor TSH and FT4 before each cycle. Consider consultation with endocrinologist.	Not recommended.	Initiate levothyroxine therapy at 0.5-1.5 mcg/kg if no heart disease or severe co-morbidities; otherwise, start at 12 to 25mcg daily and increase dose slowly (no sooner than every 4-6 weeks)¥.	Consider holding therapy until symptoms are controlled, the patient is stable on hormone therapy, and is receiving <7.5 mg of prednisone or equivalent daily.
	GRADE 3	Severe symptoms‡ Very low FT4 and TSH very high.	Monitor TSH and FT4. Hospitalization indicated.	Initiate corticosteroids at a dose of 1-2 mg/kg/day methylprednisolone IV and continue until improvement to mild severity, resolve or return to baseline. Taper over at least 1 month. Commence IV hydration if indicated.	Above plus supportive therapy for severe cardio-respiratory symptoms.	
	GRADE 4	Life-threatening Very low FT4 and TSH very high.				Discontinue therapy.

§ 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.

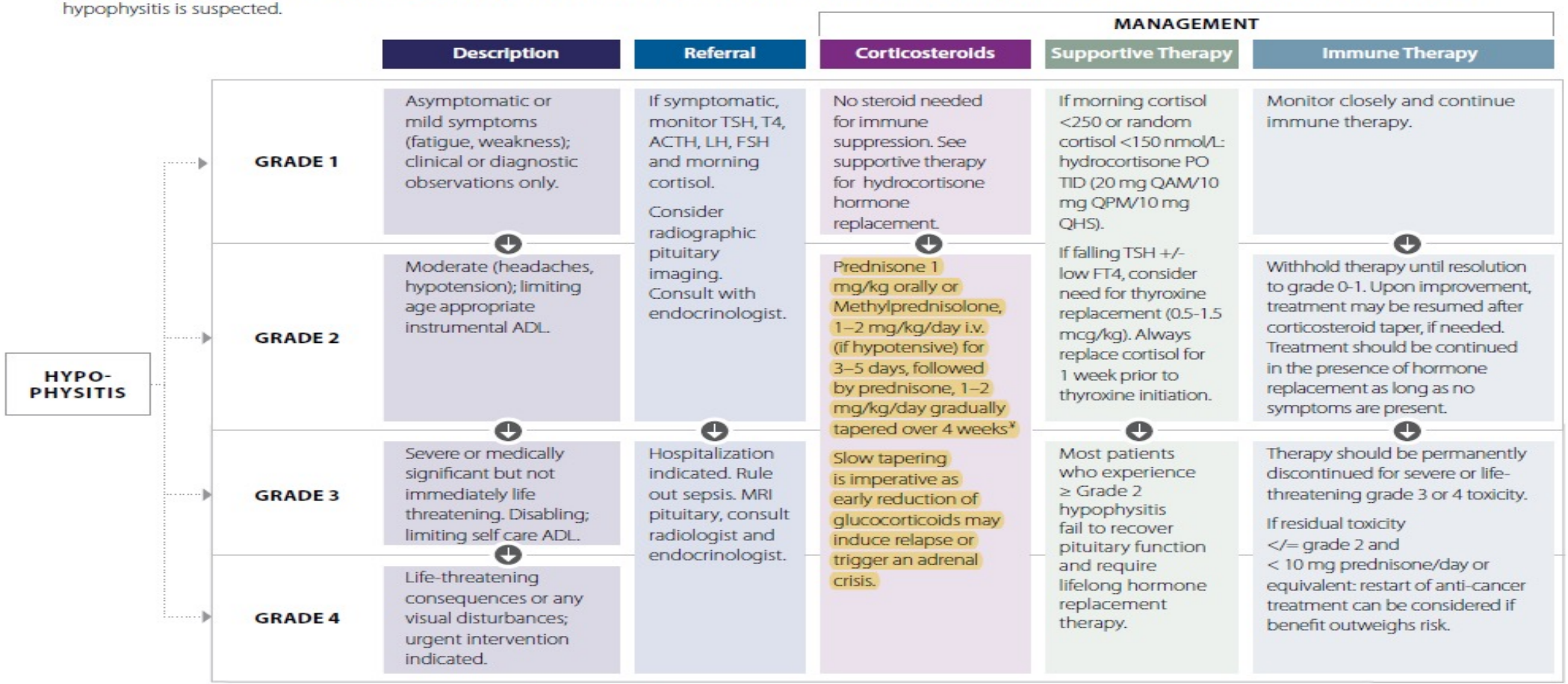
			MANAGEMENT		
	Description	Referral	Corticosteroids	Supportive Therapy	Immune Therapy
HYPER-THYROIDISM					
GRADE 1	Asymptomatic FT4 normal; TSH suppressed (<0.3mUI/L).	Monitor TSH and FT4 before each cycle.	Not recommended.	Intervention not indicated.	Monitor closely and continue immune therapy.
GRADE 2	Moderate symptoms§ Suppressed TSH (<0.1mUI/L); high FT4.	Monitor TSH and FT4 before each cycle. Consult with endocrinologist.	Consider a short period of 1 mg/kg/day PO prednisone or equivalent for acute thyroiditis presenting as hyperthyroidism.	Typically patients are asymptomatic, if symptomatic initiate an oral beta-blocker (e.g. propranolol 10-40 mg QID or atenolol 25-50 mg daily). Refer to endocrinologist for consultation.	Withhold therapy until symptoms are controlled, the patient is stable on hormone therapy, and is receiving <7.5 mg of prednisone or equivalent daily.
GRADE 3	Severe symptoms‡ Suppressed TSH (<0.1mUI/L); FT4 high.	Hospitalization indicated. Monitor TSH and FT4. Rule out sepsis.	Initiate corticosteroids at a dose of 1-2 mg/kg/day methylprednisolone IV and continue until improvement to mild severity, resolve or return to baseline. Taper over at least 1 month.	If urgent, consider initiating therapy with methimazole (e.g. 20-30 mg/day, reduced after 4-6 weeks to maintenance doses 5-15 mg/day) or propylthiouracil (e.g. 200-300 mg/day, then reduced to maintenance of 50-150 mg/day) in cases of Grave's disease. Initiate thyroid replacement if hypothyroid after several weeks (see management of hypothyroidism algorithm).	
GRADE 4	Life-threatening Suppressed TSH (<0.1mUI/L); FT4 high.				Discontinue therapy.

§ 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.

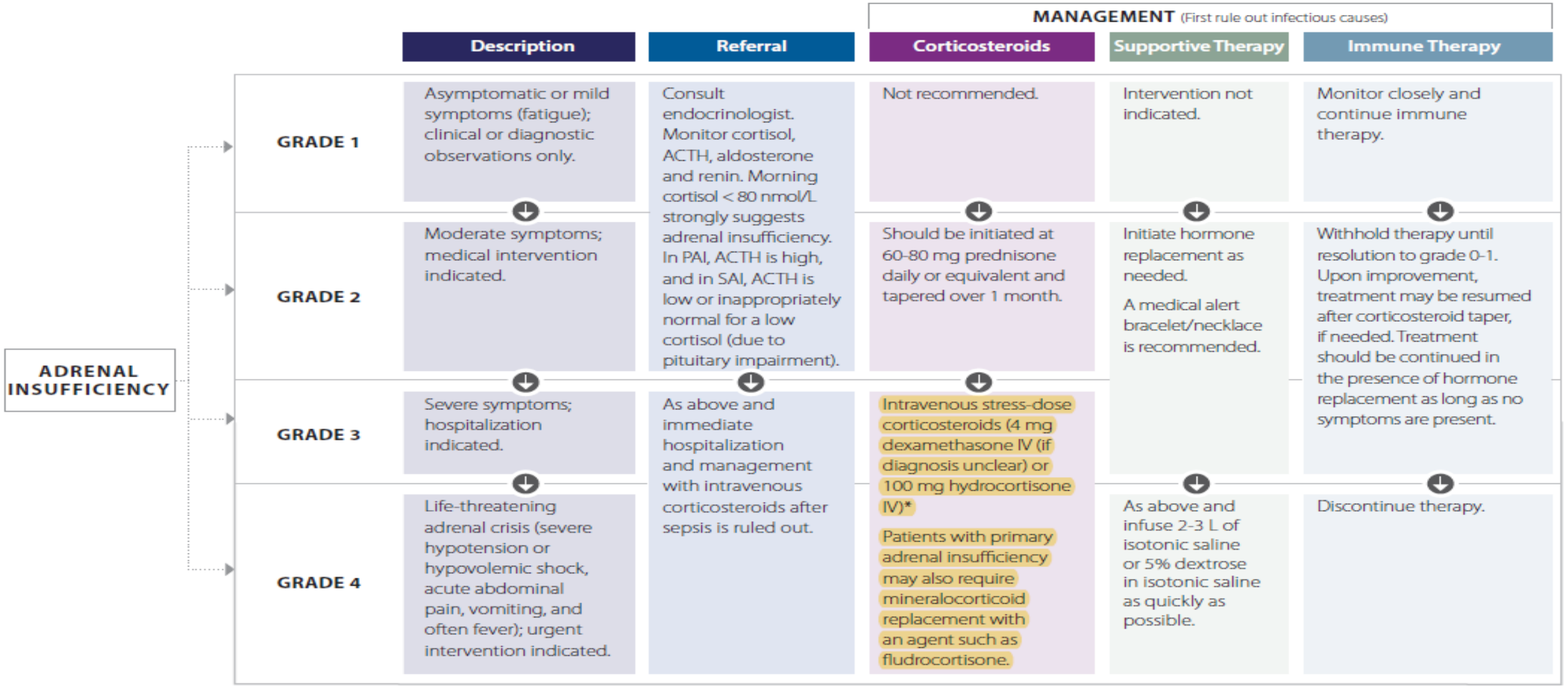


§ nonspecific symptoms such as headache, visual impairment, fatigue, weakness, confusion, memory loss, erectile dysfunction and loss of libido, anorexia, labile moods, insomnia, temperature intolerance, subjective sensation of fever, and chills.
¥ Alternatively dexamethasone, 4 mg every 6 hours for 1 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

	Description	Referral	MANAGEMENT (First rule out infectious causes and disease progression) Corticosteroids	Supportive Therapy	Immune Therapy
GRADE 1	AST/ALT up to 3 X ULN or total bilirubin up to 1.5 X ULN (or <2 X baseline).※	Not required. Consider viral serology.	Not recommended.	Not required.	Monitor closely and continue immune therapy.
GRADE 2	AST/ALT >3-5 X ULN or total bilirubin > 1.5-3 X ULN (or >2 baseline).※	Consider hepatology/ gastroenterology consult. Consider hepatitis serology.	Recheck liver function in 2-3 days & if no improvement, initiate prednisone 0.5-1 mg/kg/day PO or IV equivalent and increase if no improvement. Taper over 2-4 weeks for 0.5 mg/kg and ≥ 4 weeks for 1 mg/kg if liver function normalizes.	Not required.	Withhold therapy until resolution to grade 0-1 and prednisone ≤ 10 mg.
GRADE 3	AST/ALT > 5-20 X ULN or total bilirubin > 3-10 X ULN.※	Hepatology/ gastroenterology consult. Consider liver biopsy to rule out other causes of hepatitis.§	High dose IV steroids, methylprednisolone 1-2 mg/kg/day followed by taper with prednisone 1-2 mg/kg/day PO over ≥ 4 weeks.	If transaminases do not decrease within 3 days after steroids, add mycophenolate mofetil (MM) 500-1000 mg PO q12h; discontinue once prednisone taper to 10 mg daily. If no improvement or worsening after 7 days: consult expert or switch to another immunosuppressant.*	Permanently discontinue therapy.
GRADE 4	AST/ALT >20 X ULN or total bilirubin > 10 X ULN.※				

§ 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.

NEURO-TOXICITY	Description	Referral	MANAGEMENT: Corticosteroids	MANAGEMENT: Supportive Therapy	MANAGEMENT: Immune Therapy
GRADE 1	Asymptomatic or mildly symptomatic.	Not required.	Not required.	Not required.	Continue immunotherapy and monitor for progression of disease.
GRADE 2	New onset moderate symptoms limiting instrumental activities of daily living.	Early neurological consult is advised MRI, nerve conduction studies, lumbar puncture, electromyography may be required to assist diagnosis and to rule out other causes.※	Start oral prednisone 0.5-1 mg/kg/day or equivalent and taper over 2-4 weeks if 0.5 mg/kg and over 4 weeks if 1 mg/kg if improved. If no response, treat as grade 3-4.	If worsens or atypical presentation despite steroids, consider other immunosuppressive agents such as infliximab (5 mg/kg) or mycophenolate mofetil (500 mg BID) until resolution to grade 0-1. Some patients may require IV immunoglobulin, plasmapheresis or supportive medications.§	Withhold therapy until resolution to grade 0-1 & resume after analysis of benefit/risks; evaluate on case-by-case basis.
GRADE 3	New onset severe symptoms (e.g. vision changes, weakness affecting self-care activities of daily living or sensory deficits). Not immediately life threatening.		Start prednisone 1-2 mg/kg/day IV or equivalent and taper over at least 4 weeks once resolves to grade 0-1.		Permanently discontinue immune therapy.
GRADE 4	Life threatening consequences; urgent intervention indicated.				

§ 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.

RENAL TOXICITIES

	Description	Referral	MANAGEMENT: Corticosteroids	MANAGEMENT: Supportive Therapy	MANAGEMENT: Immune Therapy
GRADE 1	Serum creatinine > ULN and 1.5-2.0 X above baseline; proteinuria 1+, <1.0g/24h.	Not required.	Not required.	Suggest hydration and cessation of nephrotoxic drugs[§] Monitor and replace fluid/electrolyte imbalances.	Monitor serum creatinine values weekly and continue immune therapy. If creatinine worsens, treat as grade 2 or 3-4.
GRADE 2	Serum creatinine >2.0-3.0 X baseline; proteinuria 2+, 1.0-3.4g/24h.	Consider renal consultation and send urine for microscopy. Ultrasound and/or biopsy, as appropriate, to exclude non-immune causes and/or confirm immune renal toxicity.	Start prednisone 0.5-1 mg/kg daily oral or IV equivalent; once resolved to grade 0-1, taper over 2-4 weeks if 0.5 mg/kg and over 4 weeks if 1 mg/kg.	Same as above and addition of mycophenolate mofetil may be considered (has been reported in case reports in refractory cases). Hemodialysis may be required in addition to steroids if creatinine worsens (as reported in case reports).	Monitor serum creatinine q2-3 days. Withhold therapy until creatinine decreases to grade 1 & prednisone dose tapered to <10 mg/day. If creatinine increased >7days or symptoms worsen, treat as grade 3-4.
GRADE 3	Creatinine >3.0 X baseline; proteinuria >3.5g/24h.		Start methylprednisolone 1-2 mg/kg IV daily or equivalent; taper over ≥ 4 weeks once resolved to grade 0-1.		Monitor serum creatinine daily. Permanently discontinue immune therapy.
GRADE 4	Creatinine >6.0 X ULN. Life threatening consequences; dialysis indicated.				

§ I.e. aminoglycosides, contrast agent etc.

HOW CAN WE MONITOR FOR ADVERSE EVENTS RELATED TO IMMUNOTHERAPY – PROVIDER and PATIENT'S PERSPECTIVE

PRIOR TO STARTING IMMUNOTHERAPY

- ASSESS PT'S MEDICAL HISTORY FOR ANY AUTOIMMUNE DISEASE
- REVIEW AND RECORD ALL MEDICATIONS INCLUDING OTC AND HERBALS
- DOCUMENT UNDERLYNING MEDICAL CONDITIONS AFFECTING NAY ORGAN SYSTEM (PULMONARY, CARDIAC, NEUROLOGIC, MUSCULOSKELETAL
- ASSESS REPRODUCTIVE STATUS
- ASSESS SUPPORT /FAMILY STATUS
- EDUCATE PATIENT: ON IMMUNE THERAPY MOA, POTENTIAL TOXICITY PROFILE INCLUDING PRESENTING SYMPTOMS AND TIMING AND AVAILABLE RESOURCES

SYMPTOMS TO REPORT

- ANY NEW SYMPTOMS INCLUDING SEVERE FATIGUE, HEADACHE, RASH, COUGH, SOB, CHEST PAIN, ABDOMINAL BLOATING, CHANGE IN BOWEL PATTERN, WEIGHT LOSS, VISION CHANGES OR EYE PAIN, SEVERE MUSCLE WEAKNESS , SEVERE MUSCLE OR JOINT PAINS AND OR MOOD CHANGES
- IMMUNETHERAPY RELATED ADVERSE EVENTS CAN OCCUR NAFTER COMPLETON OF THERAPY AND PT SHOULD MONITOR FOR SYMPTOMS FOR 2 YEARS AFTER COMPLETION F OF THERAPY

- VACCINES THAT ARE INACTIVATED OR KILLED PREPARATIONS ARE PERMISSIBLE DURING IMMUNOTHERAPY . LIVE VACCINES ARE NOT

PRE-THERAPY ASSESSMENT	MONITORING TIMELINESS	ABNORMALS
CLINICAL: • PHYSICAL EXAM • COMPREHENSIVE HISTORY • NEUROLOGIC EXAM • BOWEL HABITS • INFECTIOUS DISEASE SCREENING	EACH VISIT ASSESS WITH CLINICAL EXAM FOR AE SYMPTOMS	FOLLOW-UP BASED ON FINDINGS OR SYMPTOMS
IMAGING: • CROSS-SECTIONAL IMAGING • BRAIN MRI (IF INDICATED)	PERIODIC IMAGING AS INDICATED	FOLLOW UP TESTING AS INDICATED BASED ON IMAING FINDINGS
GENERAL BLOODWORK • CBC/PL/DIFF • CMP	REPEAT PRIOR TO EACH TREATMENT OR EVERY 4 WEEKS DURING IMMUNOTHERAPY , THEN 6—12 WEEKS OR AS INDICATED	HbA1c FOR ELEVATED GLUCOSE
DERMATOLOGIC: • SKIN EXAM	REPEAT AS NEEDED BASED ON SYMPTOMS	MONITOR AFFECTED BSA AND LESION TYPE: PHOTOGRAPHIC DOCUMENTATION.SKIN BIOPSY IF INDICATED
THYROID • TSH/FREE T4	EVERY 4-6 WEEKS DURING IMMUNOTHERAPY AND THEN FOLLOW	TOTAL T3 AND FREE T4 IF ABNORMAL FUNCTION THYROID IS SUSPECTED

PRE-THERAPY ASSESSMENT	MONITORING TIMELINESS	ABNORMALS
ADRENAL/PITTUITARY: • ADRENAL: SERUM CORTISOL (MORNING PREFERRED) • PITUITARY: TSH, FREE T4	REPEAT PRIOR TO EACH TREATMENT OR EVERY 4 WEEKS DURING IMMUNOTHERAPY, THEN FOLLOW UP EVERY 6-12 WEEKS REPEAT CORTISOL AFTER SURGERY	LH, FSH, TESTOSTERONE (MALES), ESTRADIOL(FEMALES), ACTH
PULMONARY • OXYGEN SATURATION (RESTING AND WITH AMBULATION • PFTs FOR HIGH-RISK PATIENTS	REPEAT O2 SAT TESTS BASED ON SYMPTOMS	CHEST CT WITH CONTRAST TO EVALUATE FOR PNEUMONITIS , BIOPSY IF NEEDED TO EXCLUDE OTHER CAUSES
CARDIOVASCULAR • CONSIDER BASELINE EKG • INDIVIDUALIZED ASSESS IN CONSULT WITH CARDIOLOGY IF INDICATED	CONSIDER PERIODIC TESTING FOR THOSE WITH ABNORMAL BASELINE	INDIVIDUALIZED FOLLOW UP IN CONJUNCTION WITH CARDIOLOGY
PANCREATIC • BASELINE TESTING NOT REQUIRED	NO ROUTINE MONITORING NEEDED IF SYMPTOMATIC	AMYLASE, IPASE AND CONSIDER ABDOMINAL CT WITH CONTRAST OR MRCP FOR SUSPECTED PANCREATITIS
MUSCOLOSKELETAL • JOINT EXAM/FUNCTIONAL ASSESSMENT AS NECESSARY FOR PTS WITH PRE-EXISTING DISEASE	NO ROUTINE MONITORING NEEDED IF ASYMPTOMATIC	CONSIDER RHEUMATOLOGY REFERRAL. DEPENDING ON CLINICAL SITUATION, CONSIDER: CRP, ESR, OR CPK

Conclusions

- Immunotherapy has revolutionized the treatment of many different types of cancers
- The management of most immune-related adverse effects requires prompt referral, assessment and treatment; patient education is critical.
- We must be prepared to recognize and treat immune-related adverse events, which can be unpredictable and severe.
- Best care practice model, should include a multi-disciplinary team – including specialists in Ophthalmology, Endocrinology, Pulmonology, Gastroenterology, Cardiology, Nephrology and others.
- Interruption and steroids are the main treatments of ir-AE management to-date.

Thank You

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

NCI Cancer Center
A Cancer Center Designated by the National Cancer Institute