Management of Immune Checkpoint Inhibitor Toxicities – Adult – Inpatient/Ambulatory/Emergency Department Clinical Practice Guideline

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Content Expert(s):
Name: Elizabeth Dow, PharmD, BCOP - Pharmacy
Phone Number: (608) 265-1650
Email Address: edow@uwhealth.org

Contact for Changes:
Name: Philip Trapskin, PharmD, BCPS - Pharmacy
Phone Number: (608) 263-1328
Email Address: ptrapskin@uwhealth.org

Guideline Author(s):
Jason Bergsbaken, PharmD, BCOP – Pharmacy
Elizabeth Dow, PharmD, BCOP, BCPS – Pharmacy
Daniel Kapp, PharmD – Pharmacy
Ticiana Leal, MD – Hematology/Oncology
Catherine Renna, PharmD – Pharmacy

Reviewer(s):
Mark Albertini, MD – Medicine – Hematology/Oncology
Diane Elson, MD – Endocrinology
Mary Mably, RPh, BCOP – Pharmacy

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Chemotherapy Council Subcommittee (05/09/2018)
Pharmacy & Therapeutics Committee (05/17/2018)

Introduction

Immune checkpoint inhibitors (ICPIs) are a class of agents approved for the treatment of cancer and act by indirectly mediating T-cell immune responses against tumors. The first ICPI, ipilimumab, was approved in 2011 for the treatment of metastatic melanoma. As of January 2018, there are 6 ICPIs approved by the FDA to treat more than 10 different malignancies.

Immune checkpoint inhibitors have a unique side effect profile and cause many different toxicities referred to as immune-related adverse events (irAEs). The most common irAEs include rash and pruritus, diarrhea and colitis, endocrine abnormalities, and liver dysfunction.[1] Less common toxicities include pneumonitis and cardiac dysfunction.[2] Toxicities are similar amongst the agents, however, incidence varies. For example, ipilimumab, a cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitor, has higher rates of irAEs than pembrolizumab and nivolumab, programmed cell death-1 (PD-1) inhibitors. The rate of grade 3 or 4 toxicities for CTLA-4 inhibitors has been 20-30% compared to 10-15% for PD-1 inhibitors.[3-5] The combination of CTLA-4 and PD-1 inhibitors has the highest rates of irAEs.[1] However, these can occur at any time during treatment and can be seen as a late toxicity, even after discontinuation of therapy. Most toxicities occur within weeks to 3 months after initiation of ICPIs. Most irAEs are mild in severity; however, some can progress and become severe enough to require hospital admission, discontinuation of the agent, and death. For the most part, severe and life-threatening toxicities can be avoided if identified early and managed appropriately and, fortunately, the rate of treatment-related death is ≤2%.[4,6]

Scope

Intended User(s): Physicians, advanced practice providers, pharmacists, and registered nurses

Objective(s): To provide clinicians with the most effective therapeutic recommendations for monitoring, identification, grading, and treatment to optimize management of irAEs

Target Population: Adult patients in the following settings: inpatient, emergency department, ambulatory clinics

Clinical Questions Considered:

- When should immune checkpoint inhibitor therapy be continued, held, and resumed?
- What is the starting dose of steroids for irAEs?
- How long should corticosteroids be tapered over?
- When is the patient considered to have steroid-refractory toxicity?
- What are treatment options for steroid-refractory toxicities?

Definitions

Table 1. Abbreviations	
ACTH: adrenocorticotropic hormone	ICPI(s): immune checkpoint inhibitor(s)
CBC: complete blood count	irAE(s): immune-related adverse event(s)
CMP: complete metabolic panel	IV: intravenous
CMV: cytomegalovirus	LFTs: liver function tests
CRP: C-reactive protein	LH: luteinizing hormone
CTCAE: Common Terminology Criteria for Adverse Events	By mouth: PO
CTLA-4: cytotoxic T-lymphocyte antigen-4	PD-1: programmed cell death-1
ESR: erythrocyte sedimentation rate	PD-L1: programmed cell death ligand 1
FSH: follicle stimulating hormone	TSH: thyroid stimulating hormone
HRT: hormone replacement therapy	

1. Hypothyroidism: Low free T4 with elevated TSH or TSH > 10 with normal free T4[7]
2. Prednisone equivalents
    a. Corticosteroid recommendations in the guideline are referred to in Prednisone equivalents
    b. For ease of conversion from intravenous to oral route, a 1:1 conversion is appropriate

Table 2. Corticosteroid Equivalents

Corticosteroid	Equivalent Dose (mg)
Prednisone	5
Methylprednisolone	4
Dexamethasone	0.75-1
Hydrocortisone	20

3. Pancreatitis defined as the presence of 2 of the following 3 features:[1]
    a. Clinical symptoms
    b. Radiographic findings of inflamed pancreas
    c. Elevated amylase and lipase
4. Pituitary axis blood tests[7]
    a. 9 am cortisol (or random if unstable patient)
    b. ACTH, TSH/free T4, LH, FSH
    c. Oestradiol if premenopausal women
    d. Testosterone in men
    e. Prolactin
5. Topical steroid potency

Table 3. Potency of Common Topical Corticosteroids[8]

Potency (level)	Intensity	Medication Name	Dosage vehicle	Strength
Least potent (VII)	Mild	Hydrocortisone	C, L, O	0.5-2.5%
Low (VI)		Desonide	G, L, O	0.05%
		Fluocinolone acetonide	C	0.01%
Medium (IV and V)	Moderate	Betamethasone valerate	C, L	0.1%
		Fluocinolone acetonide	C, O	0.025%
		Fluticasone propionate	C	0.005%
		Mometasone furoate	C, L, O	0.1%
		Triamcinolone	C, L, O	0.025-0.1%
Medium to high (III)		Betamethasone dipropionate	C	0.05%
		Fluticasone propionate	O	0.005%
		Triamcinolone	C, O	0.5%
High (II)	High	Augmented betamethasone dipropionate	C, L	0.05%
		Betamethasone dipropionate	O	0.05%
		Fluocinonide	C, G, O	0.05%
Ultra-high (I)		Augmented betamethasone dipropionate	G, O	0.05%
		Clobetasol	C, G, L, O	0.05%
		Fluocinonide	C	0.1%
		Halobetasol	C, O	0.05%

C=cream, G=gel, L=lotion, O=ointment

Recommendations

General – Immune-related adverse events

1. Patients should be evaluated for risk of developing irAE prior to starting ICPI therapy[7] *(UW Health GRADE low quality evidence, strong recommendation)*
2. Patients, family, and caregivers should receive education about ICPI mechanism of action and toxicity profile prior to starting therapy and throughout treatment[7,9] *(UW Health GRADE low quality evidence, strong recommendation)*
3. Suspected irAEs should be evaluated to rule out other etiologies[7] *(UW Health GRADE low quality evidence, strong recommendation)*
4. Confirmed irAEs should be managed based on severity and grading[7] *(UW Health GRADE low quality evidence, strong recommendation)*
    4.1. All irAEs should be graded using the most updated version of CTCAE[7,10] *(UW Health GRADE low quality evidence, strong recommendation)*
5. Corticosteroid use in the management of irAEs
    5.1. Corticosteroids may be administered for most grade ≥2 toxicities[9] *(UW Health GRADE low quality evidence, weak recommendation)*
    5.2. Corticosteroid doses are provided in prednisone equivalents. Corticosteroid dose equivalents should be used when appropriate[9] *(UW Health GRADE low quality evidence, strong recommendation)*
        5.2.1. NOTE: for ease of conversion from IV to oral route, a 1:1 conversion is appropriate
    5.3. Consider corticosteroid taper when symptoms improve to grade ≤1[9] *(UW Health GRADE low quality evidence, weak recommendation)*
    5.4. If symptoms worsen, re-escalate corticosteroid dose to last dose resulting in stable or improvement in toxicity[7] *(UW Health GRADE low quality evidence, weak recommendation)*
6. ICPI treatment may be resumed at the discretion of the treating provider if all of the following are true[11] *(UW Health GRADE low quality evidence, weak recommendation)*
    6.1. irAE reverts to grade 1 or improves to baseline
    6.2. Systemic steroid dose is reduced to ≤ 10 mg per day prednisone or equivalent
    6.3. Absence of other concurrent immunosuppressive agents for treatment of irAEs
7. ICPI treatment may be permanently discontinued at the discretion of the treating provider for the following irAEs[11] *(UW Health GRADE low quality evidence, strong recommendation)*
    7.1. Life-threatening (grade 4) toxicities
        7.1.1. In general, grade 4 toxicities warrant permanent discontinuation, with the exception of endocrinopathies that have been controlled by hormone replacement[9] *(UW Health GRADE low quality evidence, weak recommendation)*
    7.2. Moderate to severe (grade 2-3) toxicities that require prolonged steroid taper (>3 months) or flare during steroid taper
8. Refer to toxicity-specific treatment for better guidance on appropriateness of ICPI rechallenge[9] *(UW Health GRADE low quality evidence, weak recommendation)*
9. Supportive care
    9.1. Pneumocystis jiroveci prophylaxis should be considered in patients anticipated to receive ≥20 mg daily of prednisone or equivalent for ≥4 weeks[12] *(UW Health GRADE low quality evidence, strong recommendation)*
    9.2. Gastrointestinal prophylaxis in high risk patients or in patients receiving high dose corticosteroids (≥1 mg/kg prednisone or equivalent)[13] *(UW Health GRADE low quality evidence, weak recommendation)*

9.3. Blood glucose monitoring should be considered in patients on corticosteroids[7] *(UW Health GRADE low quality evidence, weak recommendation)*
9.4. Vitamin D and calcium monitoring may be considered in patients on corticosteroids[7] *(UW Health GRADE low quality evidence, weak recommendation)*
9.4.1. Vitamin D and calcium supplementation may be considered in patients with prolonged corticosteroid use[9] *(UW Health GRADE low quality evidence, weak recommendation)*

Skin Toxicities

Diagnostic work-up of skin toxicities

1. Alternative etiologies such as infection, adverse effects from another drug, or contact dermatitis should be ruled out[7] *(UW Health GRADE low quality evidence, strong recommendation)*
2. Consider directed serologic studies if an autoimmune condition is suspected such as lupus or dermatomyositis[9] *(UW Health GRADE low quality evidence, weak recommendation)*
3. Consider skin biopsy for grade ≥2 toxicity[7,9] *(UW Health GRADE low quality evidence, weak recommendation)*
4. A full review of patient medications should be completed to rule out other drug-induced causes[9] *(UW Health GRADE low quality evidence, weak recommendation)*
5. Dermatology consultation may be considered for grade 2-3 and should be considered for grade 4 skin toxicities[7] *(UW Health GRADE low quality evidence, strong recommendation)*
6. Dermatologic emergencies such as Stevens-Johnson syndrome/toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms, and Sweet syndrome should be ruled out[7] *(UW Health GRADE low quality evidence, strong recommendation)*

Management of rash and dermatitis

1. General management for all grades
   1.1 Nonpharmacological interventions should be employed in all patients[7] *(UW Health GRADE low quality evidence, strong recommendation)*
      1.1.1 Educate patients to avoid skin irritants and sun exposure; topical emollients are recommended
   1.2 Topical or oral antihistamines such as diphenhydramine and hydroxyzine hydrochloride should be used for itching[1,7] *(UW Health GRADE low quality evidence, strong recommendation)*
      1.2.1 Diphenhydramine 1-2% cream, apply topically to affected area 3-4 times per day as needed for itching
      1.2.2 Diphenhydramine 25-50 mg PO every 4-6 hours needed for itching
      1.2.3 Hydroxyzine 25 mg PO 3-4 times per day as needed for itching
2. Grade 1
   2.1 ICPI treatment may be continued[7] *(UW Health GRADE low quality evidence, strong recommendation)*
   2.2 Mild to moderate potency topical corticosteroid creams may be used for localized itching or rash[7,8] *(UW Health GRADE low quality evidence, strong recommendation)*
      3.1.1 See Table. 3 Potency of Common Topical Corticosteroids
3. Grade 2
   3.1 ICPI treatment may be continued; however, skin toxicity should be monitored weekly[7,9] *(UW Health GRADE low quality evidence, weak recommendation)*
      3.1.1 If symptoms worsen or persist for 1-2 weeks, ICPI treatment should be withheld[7,9] *(UW Health GRADE low quality evidence, strong recommendation)*

3.1.1.1 If symptoms worsen or persist for 1-2 weeks despite withholding ICPI treatment, systemic corticosteroids may be considered[9] *(UW Health GRADE low quality evidence, weak recommendation)*

3.1.1.2 Prednisone 1 mg/kg once daily PO for 3 days then taper over at least 4 weeks may be considered[7,9] *(UW Health GRADE low quality evidence, weak recommendation)*

3.2 Moderate to high potency topical corticosteroid creams may be used for localized itching or rash[7,8] *(UW Health GRADE low quality evidence, strong recommendation)*

3.2.1.1 See Table. 3 Potency of Common Topical Corticosteroids

4. Grade 3

4.1 ICPI treatment should be withheld and may be permanently discontinued[1,2,7] *(UW Health GRADE low quality evidence, weak recommendation)*

4.2 High intensity topical corticosteroid creams may be used for localized itching or rash (See Table. 3 Potency of Common Topical Corticosteroids)[7,8] *(UW Health GRADE low quality evidence, strong recommendation)*

4.3 Systemic corticosteroids should be initiated[7,9] *(UW Health GRADE low quality evidence, weak recommendation)*

4.3.1 Prednisone 1-2 mg/kg IV or PO once daily may be considered[7] *(UW Health GRADE low quality evidence, weak recommendation)*

4.3.1.1 Corticosteroids should be tapered over at least 4 weeks when skin toxicity improves to baseline[2,7] *(UW Health GRADE low quality evidence, weak recommendation)*

5. Grade 4

5.1 Hospital admission is recommended[9] *(UW Health GRADE low quality evidence, strong recommendation)*

5.2 Dermatology consultation is recommended[9] *(UW Health GRADE low quality evidence, strong recommendation)*

5.3 ICPI treatment should be withheld and may be permanently discontinued[1,2,7] *(UW Health GRADE low quality evidence, weak recommendation)*

5.4 High intensity topical corticosteroid creams may be used for localized itching or rash (See Table. 3 Potency of Common Topical Corticosteroids)[7,8] *(UW Health GRADE low quality evidence, strong recommendation)*

5.5 Systemic corticosteroids should be initiated[7,9] *(UW Health GRADE low quality evidence, weak recommendation)*

5.5.1 Prednisone 1-2 mg/kg IV or PO once daily may be considered[7] *(UW Health GRADE low quality evidence, weak recommendation)*

5.5.1.1 Corticosteroids should be tapered over at least 4 weeks when skin toxicity improves to baseline[2,7] *(UW Health GRADE low quality evidence, weak recommendation)*

6. Rechallenge ICPI after skin toxicity

6.1 Consider alternative antineoplastic therapy over resuming ICPI if skin toxicity does not resolve to grade ≤1. If ICPI is only treatment option, consider restarting once resolved to grade 1[9] *(UW Health GRADE low quality evidence, weak recommendation)*

Table 4. Summary of Recommendations for Management of Skin Toxicities						
	Grade	ICPI Therapy	Corticosteroids			Comments
				Dose/Day*	Taper	
Rash Dermatitis	1	Continue	NR	-	-	
	2	Continue/Hold	Consider	1 mg/kg	≥4 weeks	Consider steroids for persistent symptoms
	3	Hold	Initiate	1-2 mg/kg	≥4 weeks	
	4	Hold or Permanently discontinue	Initiate	1-2 mg/kg	≥4 weeks	Hospital admission Dermatology consultation
*Doses reported in prednisone equivalents Abbreviations: ICPI, immune checkpoint inhibitor; NR, not recommended						

Diarrhea/colitis

Diagnostic work-up of diarrhea/colitis

1. Consider CBC, CMP, magnesium, phosphate, TSH, ESR, and CRP[9] *(UW Health GRADE low quality evidence, weak recommendation)*
2. Alternative etiologies such as infection or disease progression should be ruled out[7] *(UW Health GRADE low quality evidence, strong recommendation)*
   2.2 Consider culture and/or stool analysis for enteropathogens (*Clostridium difficile*, enteric bacterial pathogens, CMV or other viral pathogens, ova and parasitic infections) for all patients[7,9] *(UW Health GRADE low quality evidence, strong recommendation)*
3. Consider testing for lactoferrin and calprotectin[9] *(UW Health GRADE low quality evidence, weak recommendation)*
4. Consider imaging of the abdomen and pelvis[9] *(UW Health GRADE low quality evidence, weak recommendation)*
5. Consider endoscopy/sigmoidoscopy/colonoscopy with biopsy in patients without clear etiology for diarrhea or with severe diarrhea or persistent grade 2 diarrhea[7,9] *(UW Health GRADE low quality evidence, strong recommendation)*
6. Gastroenterology consultation is recommended for grade ≥2[9] *(UW Health GRADE low quality evidence, strong recommendation)*

Management of diarrhea/colitis immune-related toxicity

1. Grade 1
   1.1 ICPI treatment may be continued[7] *(UW Health GRADE low quality evidence, strong recommendation)*
   1.2 Monitor for dehydration and consider increase in oral fluid intake and other dietary changes[7,9,14] *(UW Health GRADE low quality evidence, strong recommendation)*
   1.3 Antidiarrheal agents may be considered if infection has been ruled out[7] *(UW Health GRADE low quality evidence, strong recommendation)*
      1.3.1 Antidiarrheal agents should be used with caution and with careful monitoring due to the risk of GI perforation
      1.3.2 Use of antidiarrheal agents should be avoided in patients with suspected GI perforation
      1.3.3 Examples of antidiarrheal agents include
         1.3.3.1 Loperamide 2 mg tablets, 1-2 tablets PO every 6 hours as needed up to 8 tablets per day
         1.3.3.2 Diphenoxylate-atropine 2.5-0.025 mg tablets or diphenoxylate-atropine 2.5-0.025 mg/5 mL, every 6 hours as needed up to 20 mg of diphenoxylate per day

1.4 Treatment may be escalated to grade 2, if grade 1 toxicity persists for >14 days[9] *(UW Health GRADE low quality evidence, weak recommendation)*

2. Grade 2
   - 2.1 ICPI treatment should be withheld[7] *(UW Health GRADE low quality evidence, weak recommendation)*
     - 2.1.1 May consider permanently discontinuing CTLA-4 agents[9] *(UW Health GRADE low quality evidence, weak recommendation)*
   - 2.2 Monitor for dehydration and consider increase in oral fluid intake and other dietary changes[7,9,14] *(UW Health GRADE low quality evidence, strong recommendation)*
   - 2.3 Antidiarrheal agents may be considered if infection is ruled out[7] *(UW Health GRADE low quality evidence, weak recommendation)*
     - 2.3.1 Antidiarrheal agents should be used with caution and with careful monitoring due to the risk of GI perforation
     - 2.3.2 Use of antidiarrheal agents should be avoided in patients with suspected GI perforation
   - 2.4 Systemic corticosteroids should be initiated unless diarrhea is transient[7] *(UW Health GRADE low quality evidence, strong recommendation)*
     - 2.4.1 Prednisone 1 mg/kg once daily PO[7,9,15] *(UW Health GRADE low quality evidence, weak recommendation)*
       - 2.4.1.1 If no improvement in 3 days after initiation of corticosteroids, treatment should be escalated to grade 3[2] *(UW Health GRADE low quality evidence, weak recommendation)*
     - 2.4.2 Corticosteroids may be tapered over 4-6 weeks once symptoms resolve to grade 1[2] *(UW Health GRADE low quality evidence, weak recommendation)*
3. Grade 3
   - 3.1 Consider hospital admission for patients with dehydration or electrolyte imbalance[9] *(UW Health GRADE low quality evidence, weak recommendation)*
   - 3.2 ICPI treatment should be withheld[7] *(UW Health GRADE low quality evidence, weak recommendation)*
   - 3.3 Monitor for dehydration and consider increase in oral fluid intake and other dietary changes[7,9,14] *(UW Health GRADE low quality evidence, strong recommendation)*
   - 3.4 Systemic corticosteroids should be initiated[7,15] *(UW Health GRADE low quality evidence, strong recommendation)*
     - 3.4.1 Prednisone 1-2 mg/kg IV or PO once daily may be considered[7,15] *(UW Health GRADE low quality evidence, weak recommendation)*
       - 3.4.1.1 If symptoms persist ≥3-5 days despite oral prednisone, consider administering prednisone IV[9] *(UW Health GRADE low quality evidence, weak recommendation)*
       - 3.4.1.2 If symptoms persist ≥3-5 days despite IV prednisone, consider administering noncorticosteroid (see Steroid-refractory Colitis)[9] *(UW Health GRADE low quality evidence, weak recommendation)*
   - 3.5 Corticosteroid may be switched to oral after improvement in symptoms[7] *(UW Health GRADE low quality evidence, weak recommendation)*
   - 3.6 Corticosteroids may be tapered over at least 4-6 weeks[9] *(UW Health GRADE low quality evidence, weak recommendation)*
4. Grade 4
   - 4.1 Hospital admission is recommended[9] *(UW Health GRADE low quality evidence, strong recommendation)*
   - 4.2 ICPI treatment should be permanently discontinued[9] *(UW Health GRADE low quality evidence, weak recommendation)*

4.3 Monitor for dehydration and consider increase in oral fluid intake and other dietary changes[7,9,14] *(UW Health GRADE low quality evidence, strong recommendation)*

4.4 Systemic corticosteroids should be initiated[7,15] *(UW Health GRADE low quality evidence, strong recommendation)*

4.4.1 Prednisone 1-2 mg/kg IV once daily may be considered[7,15] *(UW Health GRADE low quality evidence, weak recommendation)*

4.4.1.1 If symptoms persist ≥2-3 days, consider administering noncorticosteroid (see Steroid-refractory Colitis)[9] *(UW Health GRADE low quality evidence, weak recommendation)*

4.5 Corticosteroid may be switched to oral after improvement in symptoms[7] *(UW Health GRADE low quality evidence, weak recommendation)*

4.6 Corticosteroids may be tapered over at least 4-6 weeks[9] *(UW Health GRADE low quality evidence, weak recommendation)*

5. Steroid-refractory colitis

5.1 If no improvement in ≥3-5 days (≥2-3 days for life-threatening symptoms) after initiation of corticosteroids then infliximab may be considered[7,9] (*UW Health GRADE low quality evidence, weak recommendation)*

5.1.1 Infliximab 5 mg/kg IV for 1 dose may be considered[7,15] (*UW Health GRADE low quality evidence, weak recommendation)*

5.1.2 Infliximab may be redosed in 14 days if needed[7,15] *(UW Health GRADE low quality evidence, weak recommendation)*

5.1.3 Vedolizumab may be an alternative to infliximab[7,16] *(UW Health GRADE very low quality evidence, weak recommendation)*

5.1.4 Tacrolimus and mycophenolate may be considered in steroid- and infliximab-refractory colitis[2] *(UW Health GRADE very low quality evidence, strong recommendation)*

Table 5. Summary of Recommendations for Management of Diarrhea/Colitis

	Grade	ICPI Therapy	Corticosteroids			Comments
				Dose/Day*	Taper	
Colitis Diarrhea	1	Continue	NR	-	-	Escalate to grade 2 if symptoms persist >14 days
	2	Hold	Initiate	1 mg/kg	4-6 weeks	Escalate to grade 3 if no improvement in >3 days
	3	Hold	Initiate	1-2 mg/kg	≥4-6 weeks	Consider hospital admission Consider infliximab if symptoms worsen or persist ≥3-5 days
	4	Permanently discontinue	Initiate	1-2 mg/kg	≥4-6 weeks	Hospital admission recommended Consider infliximab if symptoms persist ≥2-3 days

*Doses reported in prednisone equivalents
Abbreviations: ICPI, immune checkpoint inhibitor; MMF, mycophenolate mofetil; NR, not recommended;

Hepatotoxicity

Diagnostic work-up of hepatitis

1. Consider LFTs and total bilirubin[9] *(UW Health GRADE low quality evidence, weak recommendation)*
2. Alternative etiologies such as infection (viral hepatitis), disease-related causes, thromboembolic events, concomitant drug administration, and alcohol abuse should be ruled out[7] *(UW Health GRADE low quality evidence, strong recommendation)*
3. Consider liver biopsy for grade ≥3[7,9] *(UW Health GRADE low quality evidence, weak recommendation)*
4. Consider hepatology consultation[7] *(UW Health GRADE low quality evidence, strong recommendation)*
   4.1 Hepatology consultation is recommended in grade 3-4[9] *(UW Health GRADE low quality evidence, strong recommendation)*

Management of hepatotoxicity secondary to immunotherapy

1. Grade 1
   1.1 ICPI treatment may be continued[7] *(UW Health GRADE low quality evidence, weak recommendation)*
   1.2 Consider monitoring LFTs and total bilirubin 1-2 times weekly[9] *(UW Health GRADE low quality evidence, weak recommendation)*
2. Grade 2
   2.1 ICPI treatment should be withheld[7] *(UW Health GRADE low quality evidence, strong recommendation)*
   2.2 If the patient is clinically stable, it is reasonable to hold off on initiation of corticosteroids and monitor transaminases and total bilirubin twice weekly[2,7] *(UW Health GRADE low quality evidence, weak recommendation)*
   2.3 Systemic corticosteroids should be initiated if there is evidence of worsening toxicity or in persistent grade 2 toxicity lasting longer than 1-2 weeks[7] *(UW Health GRADE low quality evidence, strong recommendation)*
      2.3.1 Prednisone 0.5-1 mg/kg once daily PO should be considered[7,9] *(UW Health GRADE low quality evidence, strong recommendation)*
   2.4 Consider monitoring LFTs and total bilirubin every 3 days[9] *(UW Health GRADE low quality evidence, weak recommendation)*
   2.5 Corticosteroids may be tapered over ≥4 weeks[9] *(UW Health GRADE low quality evidence, weak recommendation)*
   2.6 In persistent or worsening hepatotoxicity, ICPI treatment may be permanently discontinued[2,7] *(UW Health GRADE low quality evidence, weak recommendation)*
3. Grade 3-4
   3.1 Hospital admission is recommended[9] *(UW Health GRADE low quality evidence, weak recommendation)*
   3.2 Consider transfer to tertiary care facility[9] *(UW Health GRADE low quality evidence, weak recommendation)*
   3.3 ICPI treatment should be permanently discontinued[9] *(UW Health GRADE low quality evidence, weak recommendation)*
   3.4 Systemic corticosteroids should be initiated[7] *(UW Health GRADE low quality evidence, strong recommendation)*
      3.4.1 Prednisone 1-2 mg/kg IV or PO once daily[9] *(UW Health GRADE low quality evidence, weak recommendation)*

3.4.2 If no improvement in 2-3 days, consider mycophenolate mofetil or azathioprine (see Steroid-refractory hepatotoxicity)[9] *(UW Health GRADE low quality evidence, weak recommendation)*

3.4.2.1 NOTE: If using azathioprine, test for thiopurine methyltransferase deficiency

3.5 Corticosteroids may be tapered over 4-6 weeks[7,9] *(UW Health GRADE low quality evidence, weak recommendation)*

4. Steroid-refractory hepatotoxicity
   4.1 If symptoms worsen or persist for 2-3 days despite initiation of corticosteroids, consider mycophenolate mofetil or azathioprine[1,7,9] *(UW Health GRADE low quality evidence, weak recommendation)*
      4.1.1 Mycophenolate mofetil 1000 mg twice daily PO
      4.1.2 Azathioprine 1 mg/kg/day PO
         4.1.2.1 NOTE: If using azathioprine, test for thiopurine methyltransferase deficiency
   4.2 Higher doses of prednisone and antithymocyte globulin have been used in clinically unstable patients[17] *(UW Health GRADE very low quality evidence, weak recommendation)*
   4.3 Infliximab is contraindicated in cases of hepatitis[1,9] *(UW Health GRADE low quality evidence, strong recommendation)*

Table 6. Summary of Recommendations for Management of Hepatotoxicity

	Grade	ICPI Therapy	Corticosteroids			Comments
				Dose/Day*	Taper	
Hepatitis	1	Continue	NR	-	-	
	2	Hold	Consider	0.5-1 mg/kg	≥4 weeks	Consider steroids for worsening or persistent symptoms
	3-4	Permanently discontinue	Initiate	1-2 mg/kg	4-6 weeks	Hospital admission recommended Consider AZA/MMF if no improvement in 2-3 days

*Doses reported in prednisone equivalents
Abbreviations: AZA, azathioprine; ICPI, immune checkpoint inhibitor; MMF, mycophenolate mofetil; NR, not recommended;

Hypophysitis

Diagnostic work-up of hypophysitis

1. A pituitary axis blood test assessment should be sent[7] *(UW Health GRADE low quality evidence, strong recommendation)*
2. Evaluate morning ACTH and cortisol levels, TSH, free T4, and electrolytes[9] *(UW Health GRADE low quality evidence, weak recommendation)*
3. May consider LH, FSH, testosterone/estrogen[9] *(UW Health GRADE low quality evidence, weak recommendation)*
4. Consider brain MRI if significant symptoms or severe headache/vision changes[9] *(UW Health GRADE low quality evidence, weak recommendation)*
5. Endocrinology consultation is recommended[9] *(UW Health GRADE low quality evidence, strong recommendation)*

Management of hypophysitis

1. Grade 1-2
   1.1 ICPI may be withheld until patient is stabilized on replacement hormones[9] *(UW Health GRADE low quality evidence, weak recommendation)*

1.2 Hormonal supplementation as needed using dosing recommendations from adrenal insufficiency and hypothyroidism[9] *(UW Health GRADE low quality evidence, weak recommendation)*
1.2.1 Cortisol replacement should be administered 24-48 hours prior to initiation of levothyroxine[2,9,18] *(UW Health GRADE low quality evidence, strong recommendation)*
1.1 May consider estrogen and testosterone replacement therapy as needed in those without contraindications[9] *(UW Health GRADE low quality evidence, weak recommendation)*

2. Grade 3-4
2.1 ICPI treatment should be withheld until patient is stabilized on replacement hormones[9,19] *(UW Health GRADE low quality evidence, weak recommendation)*
2.2 Hormonal supplementation as needed using dosing recommendations from adrenal insufficiency and hypothyroidism[9] *(UW Health GRADE low quality evidence, weak recommendation)*
2.2.1 Cortisol replacement should be administered 24-48 hours prior to initiation of levothyroxine[2,9,18] *(UW Health GRADE low quality evidence, strong recommendation)*
2.3 Consider estrogen and testosterone replacement therapy as needed in those without contraindications[9] *(UW Health GRADE low quality evidence, weak recommendation)*
2.4 Consider initial pulse dose therapy with prednisone 1-2 mg/kg IV once daily[2,9,19,20] *(UW Health GRADE low quality evidence, weak recommendation)*
2.4.1 NOTE: this is for treatment of hypophysitis, not replacement corticosteroid therapy
2.5 Corticosteroids may be tapered over 1-2 weeks[9] *(UW Health GRADE low quality evidence, weak recommendation)*
2.5.1 Corticosteroids should not be discontinued[7] *(UW Health GRADE low quality evidence, strong recommendation)* [9] *(UW Health GRADE low quality evidence, weak recommendation)*
2.5.1.1 Maintenance HRT with hydrocortisone or prednisone may be considered[9] *(UW Health GRADE low quality evidence, weak recommendation)*
2.5.1.1.1 Example dosing of HRT
2.5.1.1.1.1 Hydrocortisone 10 mg PO in the morning and 5 mg PO in the afternoon
2.5.1.1.1.2 Prednisone 5 mg PO once daily

Table 6. Summary of Recommendations for Management of Hypophysitis

	Grade	ICPI Therapy	Corticosteroids			Comments
				Dose/Day*	Taper	
Hypophysitis	1-2	Hold	Consider	HRT	-	Hold ICPI until stable on replacement hormones
	3-4	Hold	Initiate	HRT	-	Consider thyroid, estrogen, and testosterone replacement
			Consider	1-2 mg/kg	1-2 weeks	Taper steroids to maintenance dose of HRT

*Doses reported in prednisone equivalents
Abbreviations: HRT, hormone replacement therapy; ICPI, immune checkpoint inhibitor; NR, not recommended

Adrenal insufficiency

Diagnostic work-up of adrenal insufficiency

1. Evaluate morning ACTH and cortisol levels[9] *(UW Health GRADE low quality evidence, weak recommendation)*
   1.1 Consider ACTH stimulation test for indeterminate results[9] *(UW Health GRADE low quality evidence, weak recommendation)*
2. Consider BMP[9] *(UW Health GRADE low quality evidence, weak recommendation)*
3. Endocrinology consultation is recommended[9] *(UW Health GRADE low quality evidence, strong recommendation)*

Management of adrenal insufficiency

1. Grade 1
   1.1 ICPI may be withheld until patient is stabilized on HRT[9] *(UW Health GRADE low quality evidence, weak recommendation)*
   1.2 Maintenance HRT with hydrocortisone or prednisone may be considered[9] *(UW Health GRADE low quality evidence, weak recommendation)*
      1.2.1 Example dosing of HRT
         1.2.1.1 Hydrocortisone 10 mg PO in the morning and 5 mg PO in the afternoon
         1.2.1.2 Prednisone 5 mg PO once daily
   1.3 Fludrocortisone 0.1 mg PO once daily may be considered for mineralocorticoid replacement[9] *(UW Health GRADE low quality evidence, weak recommendation)*
   1.4 Titrate doses up or down as symptoms dictate or as recommended by endocrinology[9] *(UW Health GRADE low quality evidence, weak recommendation)*
2. Grade 2
   2.1 ICPI may be withheld until patient is stabilized on replacement hormone therapy[9] *(UW Health GRADE low quality evidence, weak recommendation)*
   2.2 Consider corticosteroids at 2-3 times maintenance dose[9] *(UW Health GRADE low quality evidence, weak recommendation)*
   2.3 Taper corticosteroids down to maintenance dose over 5-10 days[9] *(UW Health GRADE low quality evidence, weak recommendation)*
   2.4 Maintenance HRT with hydrocortisone or prednisone may be considered[9] *(UW Health GRADE low quality evidence, weak recommendation)*
      2.4.1 Example dosing of HRT
         2.4.1.1 Hydrocortisone 10 mg PO in the morning and 5 mg PO in the afternoon
         2.4.1.2 Prednisone 5 mg PO once daily
   2.5 Fludrocortisone 0.1 mg PO once daily may be considered for mineralocorticoid replacement[9] *(UW Health GRADE low quality evidence, weak recommendation)*
   2.6 Titrate doses up or down as symptoms dictate or as recommended by endocrinology[9] *(UW Health GRADE low quality evidence, weak recommendation)*
3. Grade 3-4
   1. ICPI may be withheld until patient is stabilized on replacement hormone therapy[9] *(UW Health GRADE low quality evidence, weak recommendation)*
   2. Consider hospital admission especially if patient is hemodynamically unstable, vomiting, or unable to take medications PO[9] *(UW Health GRADE low quality evidence, weak recommendation)*
      3.2.1 Patients should be seen in clinic or the emergency department for initial management[9] *(UW Health GRADE low quality evidence, strong recommendation)*
   3. Aggressive fluid hydration with D5W, NS should be considered[9] *(UW Health GRADE low quality evidence, strong recommendation)*

3.1 Stress-dose corticosteroids should be initiated[20] *(UW Health GRADE low quality evidence, strong recommendation)*
  3.1.1 Examples include hydrocortisone 50 mg every 8 hours IV[9] *(UW Health GRADE low quality evidence, weak recommendation)*
3.2 Taper corticosteroids down to maintenance dose over 7-14 days after discharge[9] *(UW Health GRADE low quality evidence, weak recommendation)*
  3.2.1 Maintenance HRT with hydrocortisone 20-30 mg PO in the morning and 10-20 mg PO in early afternoon may be considered[9] *(UW Health GRADE low quality evidence, weak recommendation)*
3.3 Fludrocortisone 0.1 mg PO once daily may be considered for mineralocorticoid replacement[9] *(UW Health GRADE low quality evidence, weak recommendation)*
3.4 Titrate doses up or down as symptoms dictate or as recommended by endocrinology[9] *(UW Health GRADE low quality evidence, weak recommendation)*

Table 6. Summary of Recommendations for Management of Endocrinopathies

	Grade	ICPI Therapy	Corticosteroids			Comments
				Dose/Day*	Taper	
Adrenal Insufficiency	1	Hold	Consider	HRT	-	Hold ICPI until stable on HRT
	2	Hold	Consider	2-3x HRT	5-10 days	Consider fludrocortisone for mineralocorticoid replacement
	3-4	Hold	Initiate	Stress dose	7-14 days	Taper steroids to maintenance dose of HRT

*Doses reported in prednisone equivalents
Abbreviations: HRT, hormone replacement therapy; ICPI, immune checkpoint inhibitor; NR, not recommended

Hypothyroidism

Diagnostic work-up of hypothyroidism

1. Monitor TSH and free T4 every 4-6 weeks[9] *(UW Health GRADE low quality evidence, weak recommendation)*
2. Consider endocrinology consultation for all grades[9] *(UW Health GRADE low quality evidence, weak recommendation)*
   2.1 Endocrinology consultation is recommended in grade 3-4[9] *(UW Health GRADE low quality evidence, strong recommendation)*

Management of hypothyroidism

1. Grade 1
   1.1 ICPI treatment may be continued for asymptomatic elevated TSH[7,20] *(UW Health GRADE low quality evidence, weak recommendation)*
   1.2 Consider obtaining thyroid peroxidase antibodies if recommended by endocrinology[9] *(UW Health GRADE low quality evidence, strong recommendation)*
2. Grade 2-4
   2.1 ICPI treatment may be withheld[9] *(UW Health GRADE low quality evidence, weak recommendation)*
     2.1.1 ICPI treatment may be resumed after thyroid hormone replacement is stabilized[9] *(UW Health GRADE low quality evidence, weak recommendation)*
   2.2 Consider hospital admission for IV therapy is signs if myxedema (bradycardia, hypothermia)[9] *(UW Health GRADE low quality evidence, weak recommendation)*

2.3 Levothyroxine 0.5-1.5 mcg/kg PO once daily should be initiated in symptomatic patients or in asymptomatic patients with TSH levels that persist >10 mIU/L[7,9] *(UW Health GRADE low quality evidence, strong recommendation)*
  2.3.1 Starting dose of levothyroxine 25-50 mcg PO once daily may be considered in patients with cardiac history[9] *(UW Health GRADE low quality evidence, weak recommendation)*
    2.3.1.1 Starting dose of levothyroxine 12.5-25 mcg PO once daily may be considered in elderly patients[21] *(UW Health GRADE low quality evidence, weak recommendation)*

Hyperthyroidism

Diagnostic work-up of hyperthyroidism

1. Monitor TSH and free T4 every 4-6 weeks[9] *(UW Health GRADE low quality evidence, weak recommendation)*
2. Consider TSH receptor antibodies if there are clinical features and suspicion of Grave disease[9] *(UW Health GRADE low quality evidence, weak recommendation)*
3. Consider endocrinology consultation[9] *(UW Health GRADE low quality evidence, weak recommendation)*
   3.1 Endocrinology consultation is recommended in grade 3-4[9] *(UW Health GRADE low quality evidence, strong recommendation)*

Management of hyperthyroidism

1. Grade 1
   1.1 ICPI treatment may be continued[7] *(UW Health GRADE low quality evidence, weak recommendation)*
2. Grade 2
   2.1 ICPI treatment may be withheld if the patient is symptomatic[7] *(UW Health GRADE low quality evidence, weak recommendation)*
     2.1.1 ICPI treatment may be resumed when symptoms resolve or are controlled[7] *(UW Health GRADE low quality evidence, weak recommendation)*
   2.2 A beta-blocker may be considered for symptomatic relief[7] *(UW Health GRADE low quality evidence, weak recommendation)*
     2.2.1 Propranolol IR, 10-40 mg PO 3-4 times per day[22] *(UW Health GRADE low quality evidence, weak recommendation)*
     2.2.2 Atenolol, 25-100 mg PO 1-2 times per day[22] *(UW Health GRADE low quality evidence, weak recommendation)*
3. Grade 3-4
   3.1 ICPI treatment may be withheld until symptoms return to baseline[9] *(UW Health GRADE low quality evidence, weak recommendation)*
   3.2 Hospital admission may be considered[9] *(UW Health GRADE low quality evidence, weak recommendation)*
   3.3 A beta-blocker may be considered for symptomatic relief[7] *(UW Health GRADE low quality evidence, weak recommendation)*
   3.4 Prednisone 1-2 mg/kg IV once daily may be considered[7,9] *(UW Health GRADE low quality evidence, weak recommendation)*
   3.5 Taper corticosteroids over 1-2 weeks[9] *(UW Health GRADE low quality evidence, weak recommendation)*
   3.6 Methimazole or propylthiouracil may be considered[23] *(UW Health GRADE very low quality evidence, weak recommendation)*
     3.6.1 Check baseline CBC, ALT, and AST prior to initiation of therapy

4. NOTE: hyperthyroidism is often followed by hypothyroidism (see previous section for management)

Type 1 diabetes mellitus

Diagnostic work-up of diabetes mellitus

1. Monitor for hyperglycemia[9] *(UW Health GRADE low quality evidence, weak recommendation)*
2. Laboratory monitoring in suspected type 1 diabetes should include ketone urine test and anion gap assessment[9] *(UW Health GRADE low quality evidence, weak recommendation)*
3. Endocrinology consultation is recommended[9] *(UW Health GRADE low quality evidence, strong recommendation)*

Management of diabetes mellitus

1. In grade 1-2, ICPI treatment may be continued[7] *(UW Health GRADE low quality evidence, weak recommendation)*
2. In grade 3-4, ICPI treatment may be withheld until glucose control is achieve[7,19] *(UW Health GRADE low quality evidence, weak recommendation)*
3. Hyperglycemia should be management according to standard of care[7] *(UW Health GRADE low quality evidence, strong recommendation)*
4. Corticosteroids will most likely negatively impact glucose control and should be withheld[7] *(UW Health GRADE low quality evidence, weak recommendation)*

Pancreatitis

Diagnostic work-up of pancreatitis

1. Consider monitoring amylase and lipase if pancreatitis is clinically suspected[9] *(UW Health GRADE low quality evidence, weak recommendation)*

Management of Pancreatitis

1. In grade 1-2, ICPI treatment may be continued in asymptomatic patients[24] *(UW Health GRADE low quality evidence, weak recommendation)*
2. In grade 3-4, ICPI treatment may be withheld until symptoms resolve[24] *(UW Health GRADE low quality evidence, weak recommendation)*
3. Corticosteroids are not recommended in asymptomatic patients with modest elevations in amylase and lipase[9] *(UW Health GRADE low quality evidence, weak recommendation)*
4. Consider corticosteroids in symptomatic patients[1] *(UW Health GRADE low quality evidence, weak recommendation)*
5. Prednisone 1 mg/kg IV or PO once daily[1] *(UW Health GRADE low quality evidence, weak recommendation)*

Pneumonitis

Diagnostic work-up of pneumonitis

1. Alternative etiologies such as infection and disease/treatment-related causes should be ruled out[7] *(UW Health GRADE low quality evidence, strong recommendation)*
2. Consider chest x-ray, CT, pulse oximetry[7,9] *(UW Health GRADE low quality evidence, weak recommendation)*

3. Initiation of treatment should not be delayed if there is no other apparent cause or if the patient is clinically unstable[2,7] *(UW Health GRADE low quality evidence, strong recommendation)*
4. Consider bronchoscopy with bronchoalveolar lavage for grade ≥2[9] *(UW Health GRADE low quality evidence, weak recommendation)*
5. Pulmonary consultation is recommended[9] *(UW Health GRADE low quality evidence, strong recommendation)*

Management of pneumonitis

1. Grade 1
   - 1.1 ICPI treatment may be withheld[7] *(UW Health GRADE low quality evidence, weak recommendation)*
     - 1.1.1 Considering resuming ICPI with radiographic evidence of improvement[7,9] *(UW Health GRADE low quality evidence, weak recommendation)*
   - 1.2 Symptoms should be monitored every weekly[9] *(UW Health GRADE low quality evidence, strong recommendation)*
   - 1.3 If symptoms worsen or no improvement, treatment should be escalated to appropriate grade of severity[7,9] *(UW Health GRADE low quality evidence, weak recommendation)*
2. Grade 2
   - 2.1 ICPI treatment should be withheld[2,7] *(UW Health GRADE low quality evidence, strong recommendation)*
   - 2.2 Consider initiation of systemic corticosteroids[9] *(UW Health GRADE low quality evidence, weak recommendation)*
     - 2.1.1.1 Prednisone 1-2 mg/kg IV or PO once daily may be considered[7,9] *(UW Health GRADE low quality evidence, weak recommendation)*
       - 2.1.1.1.1 Taper corticosteroids over 4-6 weeks[1,7] *(UW Health GRADE low quality evidence, strong recommendation)*
     - 2.1.1.2 If no improvement in symptoms for ≥2-3 days, manage as per grade 3[7,9] *(UW Health GRADE low quality evidence, weak recommendation)*
3. Grade 3 and 4
   - 3.1 ICPI treatment should be permanently discontinued[7] *(UW Health GRADE low quality evidence, strong recommendation)*
   - 3.2 Systemic corticosteroids should be initiated[7] *(UW Health GRADE low quality evidence, strong recommendation)*
     - 3.2.1 Prednisone 1-2 mg/kg IV once daily may be considered[9] *(UW Health GRADE low quality evidence, weak recommendation)*
     - 3.2.2 If no improvement or worsening 48 hours after initiation of corticosteroids, additional immunosuppressive medications may be considered (see Steroid-refractory pneumonitis)[7,25] *(UW Health GRADE low quality evidence, weak recommendation)*
     - 3.2.3 Corticosteroids may be tapered over 4-6 weeks[7] *(UW Health GRADE low quality evidence, weak recommendation)*
4. Steroid-refractory pneumonitis
   1. If no improvement or worsening 48 hours after initiation of corticosteroids, additional immunosuppressive medications may be considered[7,25] *(UW Health GRADE low quality evidence, weak recommendation)*
      - 4.1.1 Infliximab or mycophenolate may be considered if concurrent hepatotoxicity[7] *(UW Health GRADE low quality evidence, weak recommendation)*
      - 4.1.2 Infliximab 5 mg/kg IV for 1 dose may be considered[9] *(UW Health GRADE low quality evidence, weak recommendation)*

4.1.3 Mycophenolate mofetil 1000 mg twice daily may be considered[9] *(UW Health GRADE low quality evidence, weak recommendation)*

Table 7. Summary of Recommendations for Management of Pulmonary Toxicities						
	Grade	ICPI Therapy	Corticosteroids			Comments
				Dose/Day*	Taper	
Pneumonitis	1	Hold	NR	-	-	Escalate treatment is symptoms persist
	2	Hold	Consider	1-2 mg/kg	4-6 weeks	Treat as grade 3 if symptoms persist ≥2-3 days
	3-4	Permanently discontinue	Initiate	1-2 mg/kg	4-6 weeks	Consider additional immunosuppressive agents if symptoms persist ≥48 hours
*Doses reported in prednisone equivalents Abbreviations: ICPI, immune checkpoint inhibitor; NR, not recommended						

Cardiotoxicities

Diagnostic work-up of cardiotoxicities

1. Consider checking echocardiogram and troponin at baseline[9] *(UW Health GRADE low quality evidence, weak recommendation)*
2. Consider checking troponin, CK, and BNP, echocardiogram, CXR [9] *(UW Health GRADE low quality evidence, weak recommendation)*
   2.1 Additional testing to be considered include stress test, cardiac catheterization, and cardiac MRI[9] *(UW Health GRADE low quality evidence, weak recommendation)*
3. Alternative etiologies should be ruled out[7] *(UW Health GRADE low quality evidence, weak recommendation)*
4. Cardiology consultation is recommended[7,9] *(UW Health GRADE low quality evidence, strong recommendation)*

Management of cardiotoxicities

1. ICPI therapy should be permanently discontinued[7,26] *(UW Health GRADE low quality evidence, weak recommendation)*
2. Hospital admission is recommended[9] *(UW Health GRADE low quality evidence, strong recommendation)*
   2.1 Immediate transfer to coronary care unit for patients with elevated troponin or conduction abnormalities is recommended[9] *(UW Health GRADE low quality evidence, strong recommendation)*
3. Symptom management with best standard of care[7,26] *(UW Health GRADE low quality evidence, weak recommendation)*
4. Systemic corticosteroid should be initiated[7,26] *(UW Health GRADE low quality evidence, strong recommendation)*
   4.1 Methylprednisolone 1-2 mg/kg IV once daily may be considered[26] *(UW Health GRADE low quality evidence, weak recommendation)*
5. If no response is appreciable in 24 hours, should consider early institution of cardiac transplant rejection protocol[9] *(UW Health GRADE low quality evidence, strong recommendation)*
   5.1 Should consider increase in methylprednisolone to 1000 mg IV once daily[27,28] *(UW Health GRADE low quality evidence, weak recommendation)*
   5.2 Should consider addition of either mycophenolate infliximab or antithymocyte globulin (equine)[9,28] *(UW Health GRADE very low quality evidence, weak recommendation)*

Less common irAEs

1. Providers should refer to the Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline for recommendations on the management of the following toxicities[9] *(UW Health GRADE low quality, weak recommendation)*

Table 8. Reported Immune-Related Adverse Events	
Acquired TTP	Inflammatory arthritis
Aplastic anemia	Lymphopenia
Aseptic meningitis	Myasthenia gravis
Autoimmune hemolytic anemia	Myositis
Autonomic neuropathy	Nephritis
Blepharitis	Ocular toxicities
Bullous Dermatoses	Peripheral neuropathy
Diabetes	Polymyalgia-like syndrome
Encephalitis	SCARs (SJS, TENs, DRESS)
Episcleritis	Transverse myelitis
Guillain-Barre Syndrome	Uveitis/iritis
Hemolytic uremic syndrome	Venous thromboembolism

Disclaimer

Clinical practice guidelines assist clinicians by providing a framework for the evaluation and treatment of patients. This guideline outlines the preferred approach for most patients. It is not intended to replace a clinician's judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.

Methodology

Development Process

Each guideline is reviewed and updated a minimum of every 3 years. All guidelines are developed using the guiding principles, standard processes, and styling outlined in the UW Health Clinical Practice Guideline Resource Guide. This includes expectations for workgroup composition and recruitment strategies, disclosure and management of conflict of interest for participating workgroup members, literature review techniques, evidence grading resources, required approval bodies, and suggestions for communication and implementation.

Methods Used to Collect the Evidence:

The following criteria were used by the guideline author(s) and workgroup members to conduct electronic database searches in the collection of evidence for review.

Literature Sources:

- Electronic database search (e.g., PubMed)
- Databases of systematic reviews (e.g., Cochrane Library)
- Hand-searching journals, external guidelines, and conference publications

Time Period: 2011 to 2018

Search Terms:

- (Immunotherapy OR immune check point inhibitors OR PD-1 inhibitors OR CTLA-4 inhibitors OR pembrolizumab OR nivolumab OR ipilimumab OR atezolizumab OR avelumab OR durvalumab) AND (side effect OR adverse event OR adverse reaction OR toxicity)

Methods to Select the Evidence:

- Inclusion criteria
    - Population: Human subjects ≥18 years old
    - Study design: randomized controlled trials, metaanalysis, systematic review, case series, case reports, expert opinion
    - Language: English

Methods Used to Formulate the Recommendations:

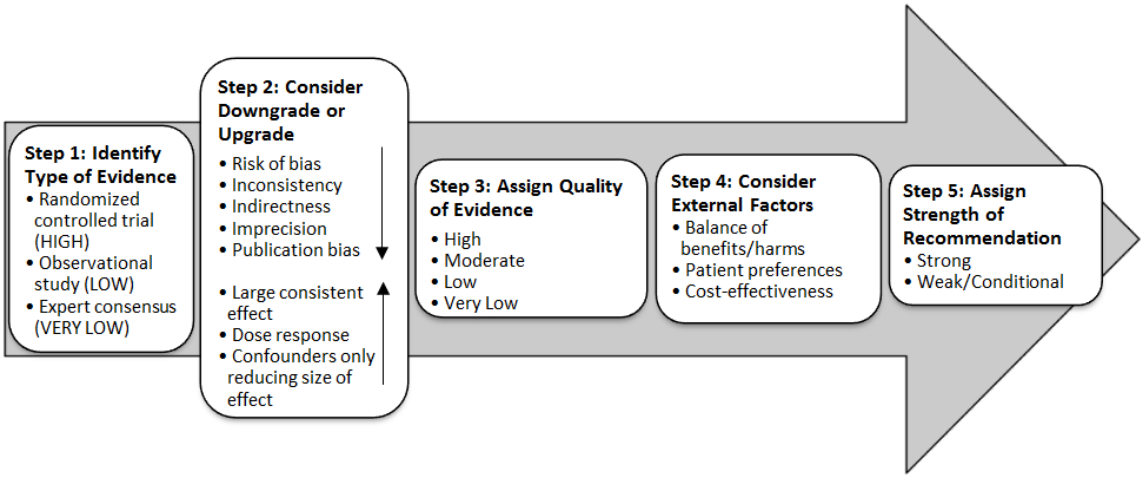
The workgroup members agreed to adopt recommendations developed by external organizations and/or created recommendations internally via a consensus process using discussion of the literature and expert experience/opinion. If issues or controversies arose where consensus could not be reached, the topic was escalated appropriately per the guiding principles outlined in the UW Health Clinical Practice Guideline Resource Guide.

Methods Used to Assess the Quality of the Evidence/Strength of the Recommendations:

Recommendations developed by external organizations maintained the evidence grade assigned within the original source document and were adopted for use at UW Health.

Internally developed recommendations, or those adopted from external sources without an assigned evidence grade, were evaluated by the guideline workgroup using an algorithm adapted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (see **Figure 1**).

Figure 1. GRADE Methodology adapted by UW Health



Rating Scheme for the Strength of the Evidence/Recommendations:

GRADE Ranking of Evidence

High	We are confident that the effect in the study reflects the actual effect.
Moderate	We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.
Low	The true effect may differ significantly from the estimate.
Very Low	The true effect is likely to be substantially different from the estimated effect.

GRADE Ratings for Recommendations For or Against Practice

Strong	The net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.
Weak/conditional	Recommendation may be conditional upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented.

Recognition of Potential Health Care Disparities:
Health care disparities exist in cancer care. Patients that are uninsured are less likely to receive proper cancer screening and express lower rates of delayed follow-up after any abnormal test results, which lead to diagnosis at more advanced stages. Furthermore, institutions most likely to serve minorities may not have as much access to state of the art diagnostic and therapeutic measures and the ability to participate in cancer clinical trials, affecting the overall quality of care. Additional factors that may influence outcomes of minorities include distrust of the health care system, stigmas related to cancer and death, literacy and language barriers, and poor expectations regarding the outcome from cancer care.

Collateral Tools & Resources

The following collateral tools and resources support staff execution and performance of the evidence-based guideline recommendations in everyday clinical practice.

Metrics

- Adherence to guideline recommendations
- Discontinuation (temporary or permanent) due to adverse drug events from immunotherapies (ie, PD/PD-L1 inhibitors, CTL-4 inhibitors)
- Inpatient use of infliximab for severe colitis associated with immunotherapies

Beacon Protocols: in development

Smart Phrases: in development

Reporting Workbench Reports
Pharmacist Immune Checkpoint Inhibitor Medication Outreach Patients [4096556]

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