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REVIEW ARTICLE

The Practice of Emergency Medicine

Diagnosis and management of immune-related adverse effects of immune checkpoint therapy in the emergency department

Sai-Ching Jim Yeung MD, PhD[1] | Aiham Qdaisat MD[1] | Patrick Chaftari MD[1] | Demis Lipe MD[1] | Jeffrey Merlin MD[1] | Eva Rajha MD[1] | Adriana Wechsler MD[1] | Marcelo Sandoval MD[1] | Jayne Viets MD[1] | Aisha Al-Breiki MD[1] | Mohsin Shah MD[2] | Ramesh Pandey MD[1] | Mona Kamal MD, PhD[3,4] | Osama Khattab MD[1] | Katy Toale PharmD[1] | Monica Wattana MD[1] | Ahmed Elsayem MD[1] | Susan Gaeta MD[1] | Patricia Brock MD[1] | Cielito Reyes-Gibby DrPH[1] | Kumar Alagappan MD[1]

[1] Department of Emergency Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

[2] Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

[3] Department of Symptom Research, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

[4] Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Ain Shams University, Cairo, Egypt

Correspondence
Sai-Ching Yeung, MD, PhD, Department of Emergency Medicine, Unit 1468, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, USA.
Email: syeung@mdanderson.org

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Abstract

Rapid advances in cancer immunotherapy using immune checkpoint inhibitors have led to significantly improved survival. Rapid identification of the toxicity syndromes associated with these therapeutic agents is very important for emergency physicians because the population of patients diagnosed with cancer is increasing and cancer therapies including immune checkpoint inhibitors have become the first-line treatment for more and more types of cancer. The emergency medicine literature lags behind rapid advances in oncology, and oncology guidelines for rapid recognition and management of these emerging toxicity syndromes are not familiar to emergency physicians. In this review article, we discuss the clinical presentation and management of immune-related adverse effects during the critical first hours of emergency care. We also suggest a workflow for the recognition and treatment of emergencies arising from serious immune-related adverse effects, including but not limited to colitis, adrenal crisis, myocarditis, pneumonitis, myasthenic crisis, diabetic ketoacidosis, bullous pemphigus, and hemophagocytic lymphohistiocytosis. Rapid advances in cancer therapy are bringing new diagnostic and therapeutic challenges to emergency providers, and therefore it is crucial to raise awareness and provide guidelines for the management of new treatment-related toxicities.

KEYWORDS
adverse events, cancer immunotherapy, emergency department, immune checkpoint inhibitors, immune-mediated

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1 | INTRODUCTION

Immune checkpoints are regulatory pathways that modulate T cell responses to presented antigens. In healthy individuals, immune checkpoint proteins mediate self-tolerance and prevent T cells from attacking normal cells indiscriminately. In the process of carcinogenesis, genomic instability may result in multiple gene mutations, and these mutations produce abnormal proteins that can be recognized as "non-self," that is, neoantigens. A hallmark of cancer is evasion of immune surveillance, and malignant cells have "learned" how to use various mechanisms to hide from the immune system, some of which involve immune checkpoints.

In recent years, antibody drugs that bind and inhibit the function of several immune checkpoint proteins (cytotoxic T lymphocyte-associated antigen 4 [CTLA-4], programmed cell death protein-1 [PD-1], and 1 of its ligands [PD-L1]) have revolutionized cancer therapy.

To date, >20 immune checkpoint inhibitors have been studied in >800 clinical trials,[1] and 7 immune checkpoint inhibitors have been approved by the US Food and Drug Administration: the anti-CTLA-4 drug ipilimumab; anti-PD-1 drugs nivolumab, pembrolizumab, and cemiplimab; and anti-PD-L1 drugs atezolizumab, avelumab, and durvalumab (Figure 1).[2] These are various types of monoclonal antibodies, and the infusion of these biologicals is associated with potential anaphylactoid reactions or infusion-related cytokine release syndrome. Boosting the immune system to treat cancer is a double-edged sword: the enhanced T cell activity attacks the cancer cells, but it often leads to autoimmune diseases as well. Immune-related adverse effects arising from immune checkpoint inhibitor therapy vary in incidence and spectrum for the immune checkpoint proteins targeted and the types of malignancy being treated, and combination therapy with different immune checkpoint inhibitors tends to cause more frequent and more severe immune-related adverse effects than monotherapy.[3–6]

Our recent retrospective review has provided an early peek at the emerging spectrum of immune-related adverse effects encountered in the emergency department (ED) setting.[7] Since the period of that review (March 1, 2011–February 29, 2016), immune checkpoint inhibitors are being increasingly used, and 4 more immune checkpoint inhibitors have been approved by the US Food and Drug Administration (Figure 1). As new agents targeting new checkpoint proteins and novel combinations of agents come into use, the relative proportions of immune-related adverse effects seen in EDs (Figure 2) may shift, but the general approach to diagnosis and management may not change significantly in the near future. Several major oncology organizations have published guidelines for diagnosis and management of immune-related adverse effects,[8–10] and 2 reviews have been published on this topic from the emergency physicians' perspective.[5,6] Being at the frontline to diagnose and treat serious immune-related adverse effects urgently in a large comprehensive cancer center, we performed this review as a department-wide effort to provide a comprehensive overview of immune-related adverse effects and to summarize our approach to diagnosing and managing immune-related adverse effects in the emergency/urgent care setting.

This review is unique in that it is a comprehensive discussion of novel syndromes of oncologic complications (ie, immune-related adverse effects) from the perspective of emergency physicians. We use tables that summarize the potential immune-related adverse effects associated with various laboratory abnormalities and clinical signs to help emergency clinicians recognize and diagnose these immune-mediated drug toxicities, adding a user-friendly reference to the emergency medicine literature.

2 | GENERAL APPROACH TO MANAGEMENT OF CANCER-RELATED IMMUNE-RELATED ADVERSE EFFECTS IN THE ED

2.1 | Clinical context

When treating a cancer patient in the ED, it is extremely important to determine the cancer diagnosis and treatment history. The chronology of symptoms relative to immune checkpoint inhibitor therapy may prompt the diagnosis. The incidence of immune-related adverse effects usually peaks at 9–12 weeks after therapy initiation (around the fourth dose) for monotherapy[11]; immune-related adverse effects have been reported to occur after the first dose,[12] but they may also occur after many months of treatment or even after treatment has stopped.[13–17] immune-related adverse effect incidence with combined immune checkpoint inhibitor therapy peaks earlier than with monotherapy.

2.2 | Triage and differential diagnosis

The Emergency Severity Index, Version 4 (ESI) has been validated for triaging adults with active cancer in the ED.[18] We suggest an initial management algorithm based on the triage of presenting acuity to guide emergency physicians in their approach for evaluation and management (Figure 3). For ESI = 1 (Figure 3A), resuscitation and stabilization of the patient follow the Advanced Cardiac Life Support protocol. For ESI = 2, a workflow using lists of immune-related adverse effects (Tables 1 and 2) highlights the immune-related adverse effects that the emergency physician may be facing and guides the grading and management (Figure 3B). Because >1 immune-related adverse effect can present concurrently, the diagnostic workup needs to be comprehensive. Therefore, most ED cancer patients with recent immune checkpoint inhibitor therapy will need >1 health care resource and will have ESI = 3. The workflow for patients with ESI ≥3 can follow Figure 3B, starting with a history and physical examination.

2.3 | Clinical assessment

To ensure early diagnosis and avoid misdiagnosis, the emergency physician should obtain as complete history as possible in regard to the patient's cancer treatment history. It is important to consider

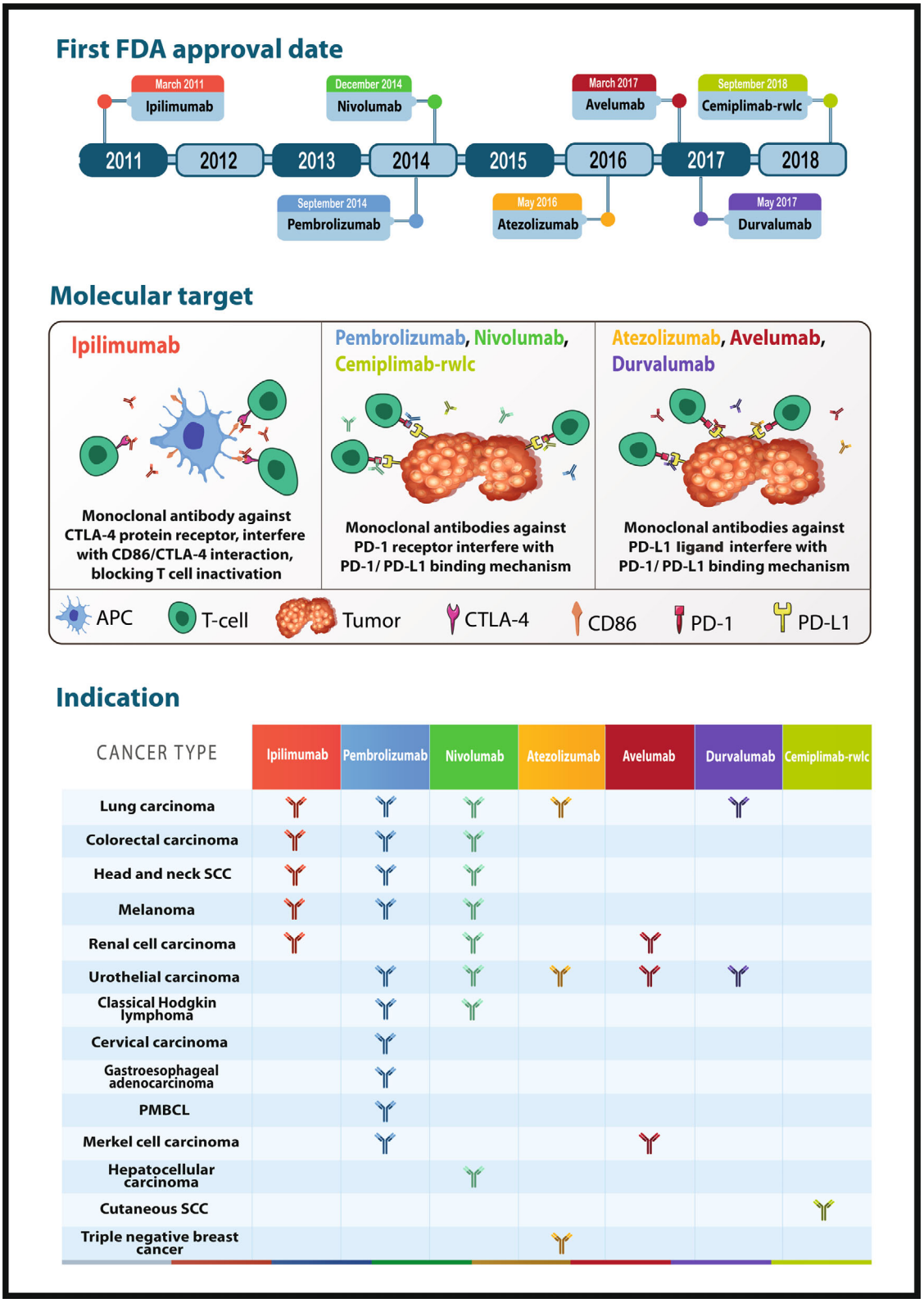


FIGURE 1 Infographic for immune checkpoint inhibitors. Upper panel: US Food and Drug Administration (FDA) approval timeline for immune checkpoint inhibitors. Middle panel: mechanism of action of immune checkpoint inhibitors. Lower panel: current FDA-approved indication for various immune checkpoint inhibitors. Abbreviations: APC, antigen-presenting cell; PMBCL, primary mediastinal B-cell lymphoma; SCC, squamous cell carcinoma

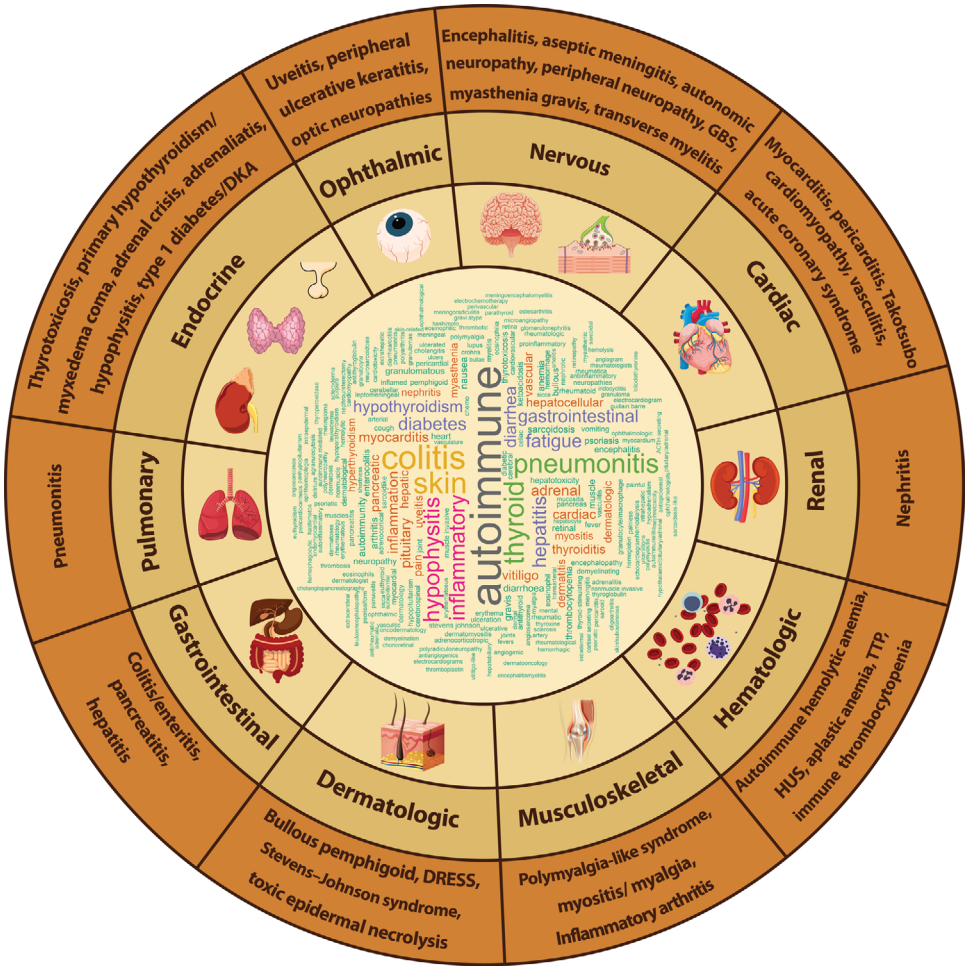


FIGURE 2 System-specific emergency immune-related adverse effects for immune checkpoint inhibitors. Word cloud showing the frequency of appearance of terms related to immune-related adverse events or immune disorders based on the abstract of publications for different approved immune checkpoint inhibitors (till December 31, 2019). Abbreviations: DKA, diabetic ketoacidosis; DRESS, Drug Rash with Eosinophilia and Systemic Symptoms; GBS, Guillain-Barré syndrome; HUS, hemolytic uremic syndrome; TTP, Thrombotic thrombocytopenic purpura

immunotherapy exposure as the etiology of an oncologic emergency, and certain presenting symptoms should ring bells for some immune-related adverse effects (Table 1). Reviews of laboratory data are imperative to detect abnormalities that may not be easily explain by the common diagnoses seen in the ED (Table 2). The role of the emergency physician regarding immune-related adverse effects is early diagnosis and appropriate grading and management based on the grade of immune-related adverse effect. Further diagnostic evaluation is often directed by the oncologists, but the emergency physician may assist in expediting care by initiating some of the work up in the ED (Supporting Information Table S1). The grading of immune-related adverse effects generally follows the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 5.0).[19] Grading and grade-based treatment considerations in the ED should be based on existing published algorithms and guidelines from the National Comprehensive Cancer Network (NCCN),[20] American Society of Clinical Oncology (ASCO),[8] Society of Immunotherapy for Cancer (SITC),[21] and European Society of Medical Oncology (ESMO).[13] Figures 4A–4H, which are based on these guidelines, was compiled to assist emergency physicians in the grading and grade-based management of various immune-related adverse effects. (A pdf for printing a poster of this figure is available for download in Appendix.)

2.4 | Clinical decision

Acute management of immune-related adverse effects with emergency-related issues may involve starting glucocorticoid therapy in the ED in consultation with the oncologist.[8,21] Most immune-related adverse effects respond to glucocorticoids, and this first-line treatment is primarily what emergency physicians will be dealing with. Second-line treatment includes immunosuppressants such as infliximab[22] or mycophenolate mofetil (specifically for hepatitis).[23] Intravenous immunoglobulins[8,24] and plasmapheresis[8] may also be used. The treatment strategy may change in the near future as clinical experience accumulates and more research is done. Disposition from the ED is based on the grade of the immune-related adverse effect.

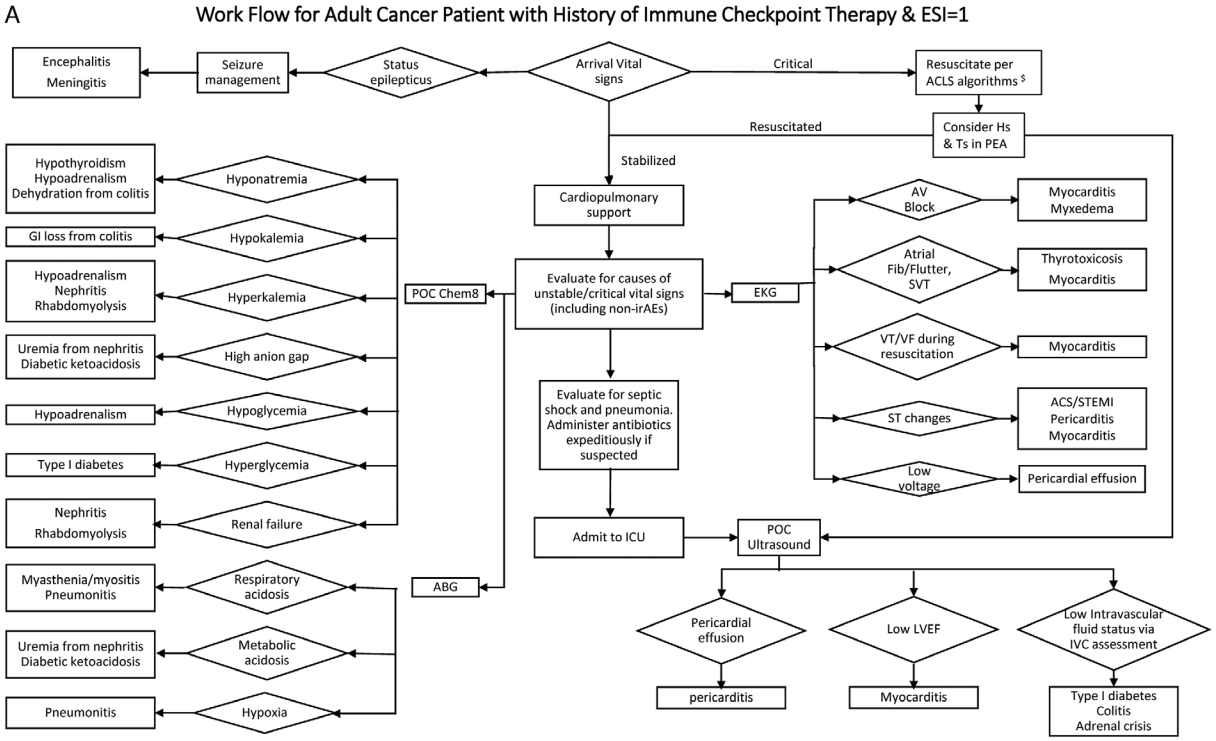


FIGURE 3 Workflow for emergency department patients who have recently received immune checkpoint therapy. (A) Emergency Severity Index, Version 4 (ESI) = 1. When considering the "H's and T's" in the resuscitation process, consider the following immune-related adverse effects as potential causes: hypovolemia (due to colitis, adrenalitis, or hypophysitis), hypoxia (due to pneumonitis, myocarditis), hydrogen ions (due to nephritis, diabetic ketoacidosis), hyperkalemia (due to nephritis, adrenalitis, hypophysitis, diabetic ketoacidosis), hypokalemia (due to colitis), hypothermia (due to thyroiditis, hypophysitis), tamponade (due to pericarditis), and thrombosis (acute coronary syndrome). After resuscitation, further bedside evaluation with point-of-care blood testing and ultrasound examination provides potential immune-related adverse effect diagnoses for further workup and guides the immediate clinical management of the cancer patient. (B) ESI = 2. Altered mental status, acute distress, and worrisome danger zone vital signs indicate level 2 in the ESI. Lists of immune-related adverse effects associated with these signs and symptoms are provided to guide expeditious care. The workflow refers to tables and figures which guide the emergency physician in narrowing down the differential diagnoses in terms of immune-related adverse effects, as well as in their grading and management. Abbreviations: ABG, arterial blood gases; ACLS, Advanced Cardiac Life Support; ACS, acute coronary syndrome; atrial fib, atrial fibrillation; AMS, altered mental status; AV, atrial-ventricular; CBC-diff, complete blood count with differential; Chem-8, basic metabolic panel; Chem-20, chemistry screen; DKA, diabetic ketoacidosis; EKG, electrocardiogram; GBS, Guillain-Barré syndrome; GI, gastrointestinal; HLH, hemophagocytic lymphohistiocytosis; ICU, intensive care unit; IV, intravenous; IVC, inferior vena cava; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PEA, pulseless electrical activity; POC, point of care; SOC, standard of care; STEMI, ST elevation myocardial infarction; SVT, supraventricular tachycardia; T1DM, type 1 diabetes mellitus; VT, ventricular tachycardia; VF, ventricular fibrillation

3 | DIAGNOSIS AND MANAGEMENT OF SPECIFIC CANCER-RELATED IMMUNE-RELATED ADVERSE EFFECTS

Exceptions to the general approach and specific issues relevant to the practice of emergency physicians for specific immune-related adverse effects are discussed below.

3.1 | Dermatologic immune-related adverse effects

Dermatologic immune-related adverse effects develop in up to 50% of patients and typically occur within the first 2 cycles of immune checkpoint inhibitor therapy.[25] These include pruritus, burning sensation, erythematous rash, alopecia, stomatitis, vitiligo, and bullous dermatitis.[3,26–28] The severity of dermatologic immune-related adverse effects is evaluated by physical examination of the skin, including the mucosal areas. Grade 3 dermatologic immune-related adverse effects include macules or papules covering >30% of the body surface area or bullous (pemphigoid) dermatitis covering >30% body surface area. Grade 4 dermatologic immune-related adverse effects include papulopustular rash associated with life-threatening superinfection, bullous dermatitis covering >30% body surface area with fluid or electrolyte abnormalities, and separation of dermis involving <10% body surface area (Steven-Johnson syndrome), 10%–30% body surface area (overlapping Steven-Johnson syndrome/toxic epidermal necrolysis) or >30% body surface area (toxic epidermal necrolysis). Incidence of high-grade dermatologic immune-related adverse effects ranges from 1%–3%, and high-dose glucocorticoids are required for treatment (Figure 4B), with the addition of pregabalin or gabapentin

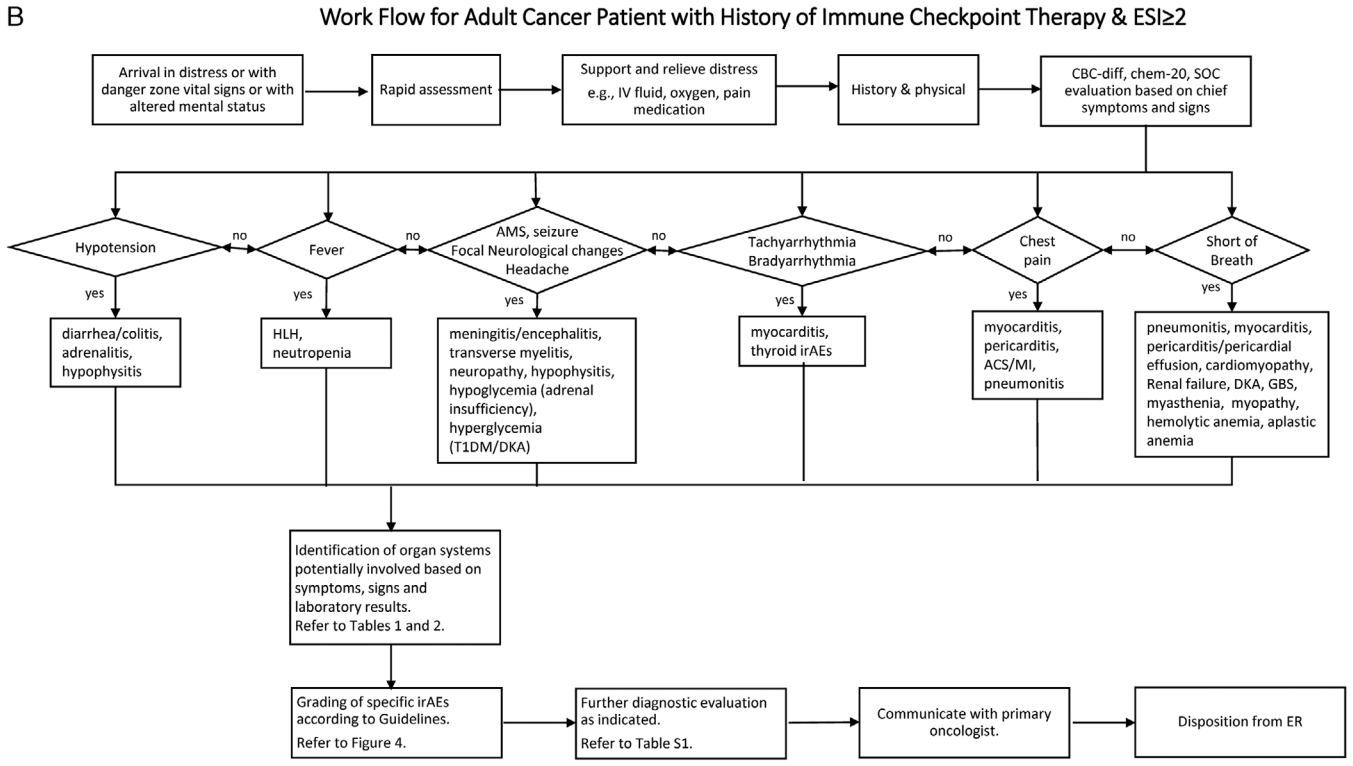


FIGURE 3 Continued

for grade 3 pruritus.[3,8,25,29] Bullae and/or Niklosky sign are warning signs, and working diagnoses of Steven-Johnson syndrome, toxic epidermal necrolysis, or drug rash with eosinophilia and systemic symptoms warrant hospital admission and emergency dermatology consultation,[30–32] because these can become fatal if not diagnosed and treated appropriately with high-dose glucocorticoids.[20] Other causes, such as infection, effects of other drugs, or a skin condition linked to another systemic disease (eg, acute febrile neutrophilic dermatosis [Sweet syndrome]), need to be excluded.

3.2 | Gastrointestinal immune-related adverse effects

Gastrointestinal immune-related adverse effects include diarrhea/enteritis, hepatitis, and pancreatitis (Figure 4C).[33] Severe colitis can occur in ~9% of patients treated with immune checkpoint inhibitors.[34] Symptoms typically occur within 5–8 weeks of initiating therapy.[35–38] Mainly, the descending colon is affected by colitis. In some cases, enteritis without any colonic involvement can lead to bowel obstruction. It is essential to exclude infectious causes of diarrhea such as *Clostridium difficile* or other pathogens. Endoscopic examination and biopsy are often needed. Glucocorticoids are the first-line treatment.[20] Dehydration and electrolyte imbalance for patients in the ED need to be treated. In case a patient with already diagnosed colitis immune-related adverse effect presents to the ED for lack of response to glucocorticoid therapy, infliximab is indicated for severe steroid-refractory colitis.[39–41] Glucocorticoids induce complete clinical remission in 37% of patients with immune-mediated enterocolitis, but this immune-related adverse effect can be serious and may rarely results in perforation or death.[37,42]

Immune-mediated hepatitis related to immune checkpoint inhibitors is detected by elevation of alanine aminotransferase or aspartate aminotransferase, with or without raised bilirubin.[21] Hepatotoxicity occurs in 2%–10% of cases; most are mild and resolve on stopping immune checkpoint inhibitors, but severe hepatic failure may occur, rarely.[8,29,43] This immune-related adverse effect usually occurs 6–14 weeks after initiation of immune checkpoint inhibitor therapy.[5,9,21,43] In the absence of specific biomarkers for immune checkpoint inhibitor-induced hepatitis, liver injury related to viral infections, alcohol and medications, or liver metastatic disease should be excluded.[29,44,45] Anti-nuclear antibodies, anti-smooth muscle antibodies, and anti-neutrophil cytoplasmic antibodies can be sent from the ED to assist the admitting team with the diagnostic workup,[8] but these results will not be available while the patient is in the ED. Imaging such as computed tomography (CT) or ultrasound to assess for possible thromboembolic or obstructive causes should be performed. Liver biopsy can be considered in complicated or unclear cases. However, initiation of therapy should not be delayed.[9] If an ED patient with transaminitis immune-related adverse effect already diagnosed and does not improve after 3–5 days of oral glucocorticoid therapy, other immunosuppressants such as mycophenolate mofetil should be considered. Unlike with other immune-related adverse effects, infliximab should be avoided because of a potential risk of liver failure.

TABLE 1 Potential serious immune-related adverse effects in the context of signs and symptoms

Presenting symptom	Warning signs	Potential immune-related adverse effect involved
Part A: neurological symptoms		
Headache	Neck stiffness	Meningitis
	Hypotension	Hypophysitis
Mental status change	Neck stiffness	Meningitis
Weakness	Respiratory failure	Guillain-Barre syndrome, Myasthenia gravis
	Paraplegia	Transverse myelitis
	Mental status change	Encephalitis
Part B: cardiopulmonary symptoms		
Chest pain	Peripheral edema	Myocarditis
	Dyspnea on exertion, pulsus paradoxus, electric alternans	Pericarditis
Cough	Hypoxia	Pneumonitis
Shortness of breath	Hypoxia	Pneumonitis
	Peripheral edema	Myocarditis
	Pulsus paradoxus, electric alternans	Pericarditis
	Pale	Hemolytic anemia, hemophagocytic lymphohistiocytosis
	Dehydration and tachypnea	Diabetic ketoacidosis
	Palpitation/irregular tachycardia	Thyrotoxicosis (Graves' disease vs thyroiditis)
Part C: gastrointestinal symptoms		
Abdominal pain	Mental status change, jaundice	Hepatitis
	Nausea and vomiting	Pancreatitis
	Diarrhea, dehydration	Colitis
	Dehydration and tachypnea	Diabetic ketoacidosis
Diarrhea	Dehydration, abdominal pain/tenderness	Colitis
Vomiting	Stiff neck, mental status change	Meningitis
	Abdominal pain	Pancreatitis
	Jaundice	Hepatitis
Part D: miscellaneous symptoms		
Vision change	Eye pain	Uveitis
Rash	Bullae with Niklosky sign	Pemphigus vulgaris
	Niklosky sign with mucosal involvement	Steven-Johnson syndrome/toxic epidermal necrolysis
Fatigue	Hypotension	Adrenal insufficiency
		Hypophysitis
	Bradycardia	Hypothyroidism
		Myocarditis
	Dehydration and tachypnea	Diabetic ketoacidosis
	Splenomegaly	Hemolytic anemia
		Hemophagocytic lymphohistiocytosis
Joint pain	Swelling, restricted movement	Arthritis

TABLE 2 Association of laboratory workup abnormalities and potential immune-related adverse effects in the emergency department

Panel	Assay	Abnormality	Associated immune-related adverse effects
Complete blood counts with differential	White blood cells (neutrophils)	Low	Neutropenia, aplastic anemia, bone marrow suppression, hemophagocytic lymphohistiocytosis
		High	Leukocytosis, bone marrow activation, autoimmune hemolytic anemia
	White blood cells (lymphocytes)	Low	Lymphopenia, bone marrow suppression
	Hemoglobin/ hematocrit	Low	Autoimmune hemolytic anemia, hemolytic uremic syndrome, aplastic anemia, colitis with bleeding, acquired hemophilia, hemophagocytic lymphohistiocytosis
	Platelets	Low	Immune thrombocytopenia, hemolytic uremic syndrome, acquired thrombotic thrombocytopenic purpura, hemophagocytic lymphohistiocytosis
Chem-7	Sodium	Low	Hypoadrenalism, hypophysitis, hypothyroidism
		High	Diabetes insipidus
	Potassium	Low	Nephritis, colitis/diarrhea
		High	Hypoadrenalism, renal failure, rhabdomyolysis, diabetic ketoacidosis
	Chloride	Low	Hypoadrenalism
	Bicarbonate	Low	DKA, lactic acidosis, severe colitis, nephritis
		High	Hypoadrenalism, severe colitis, metabolic compensation for respiratory acidosis (pneumonitis, myasthenia gravis, Guillain-Barré syndrome)
	BUN	High	Nephritis, acquired thrombotic thrombocytopenic purpura, hemolytic uremic syndrome
	Creatinine	High	Nephritis, acquired thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, sarcoidosis, lupus
	Glucose	Low	Hypoadrenalism
		High	Diabetes mellitus, diabetic ketoacidosis
Liver function tests	Albumin	Low	Hepatitis, nephrotic syndrome
	ALT	High	Hepatitis, myositis
	AST	High	Hepatitis, myositis
	LDH	High	Myositis, autoimmune hemolytic anemia, myocarditis, arthritis
	Bilirubin	High	Hepatitis, autoimmune hemolytic anemia
	Indirect bilirubin	High	Hepatitis
	Direct bilirubin	High	Hemolytic anemia
Pancreatic enzymes	Lipase	High	Pancreatitis
	Amylase	High	Pancreatitis
Cardiac enzymes and hormones	CK	High	Myositis
	CK-MB	High	Myocarditis
	Troponins	High	Myocarditis, pulmonary embolism, renal failure
	BNP	High	Myocarditis, pulmonary embolism, renal failure
Urinalysis	Urine ketone	High	Diabetic ketoacidosis, starvation ketosis due to gastrointestinal immune-related adverse effect
	Urine protein	High	Nephritis, nephrotic syndrome
	Urine blood	High	Nephritis, myositis, hemolytic uremic syndrome
Hormones	TSH[a]	Low	Hyperthyroidism, hypophysitis, central hypothyroidism
		High	Primary hypothyroidism, thyroiditis
	Free T4[a]	Low	Primary hypothyroidism, hypophysitis

(Continues)

TABLE 2 (Continued)

Panel	Assay	Abnormality	Associated immune-related adverse effects
		High	Hyperthyroid phase of thyroiditis, Graves' disease
	Cortisol[a]	Low	Primary adrenal insufficiency, hypophysitis
Coagulation profile	PT/INR	High	Hepatotoxicity, acquired thrombotic thrombocytopenic purpura
	PTT	High	Hepatotoxicity, acquired hemophilia, acquired thrombotic thrombocytopenic purpura
Calcium	Calcium	Low	Hypoparathyroidism
		High	Sarcoidosis

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CK, creatine kinase; CO_2, carbon dioxide; INR, international normalized ratio; LDH, lactic acid dehydrogenase; PT, prothrombin time; PTT, partial thromboplastin time; T4, thyroxine; TSH, thyroid stimulating hormone.

[a]Not readily available in all emergency departments.

A

In General				
	Grade			
	1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life-threatening)
General guidance for grading	Mild or no symptoms	Limiting age-appropriate ADL	Medically significant; limiting self-care; need admission	Urgent intervention needed to prevent death
	Management			
ICIs	Continue ICIs	Consider withholding ICIs	Withhold ICIs	Discontinue ICIs
Systemic corticosteroids		Prednisone equivalent (0.5-1 mg/kg/day)	Prednisone equivalent (1-2 mg/kg/day)	Prednisone equivalent (1-2 mg/kg/day)
ED disposition	Discharge	Consider hospitalization	Admit	Admit; ICU if indicated

FIGURE 4 Grading and management of immune-related adverse effects in emergency departments. (A) Grading and management of immune-related adverse effects in general. (B) Skin immune-related adverse effects. (C) Gastrointestinal immune-related adverse effects. (D) Neuromuscular immune-related adverse effects. (E) Central nervous system (CNS) immune-related adverse effects. (F) Endocrine immune-related adverse effects. (G) Heart, lung, and kidney (HLK) immune-related adverse effects. (H) Miscellaneous immune-related adverse effects. Myasthenia Gravis Foundation of America (MGFA) severity classification. Class 1: any ocular muscle weakness; may have weakness of eye closure. All other muscle strength is normal. Class 2: mild weakness affecting muscles other than ocular muscles (ocular muscle weakness of any severity may coexist). Class 3: moderate weakness affecting muscles other than ocular muscles (ocular muscle weakness of any severity may coexist). Class 4: severe weakness affecting muscles other than ocular muscles (ocular muscle weakness of any severity may coexist). Abbreviations: ADL, activity of daily living; BM, bowel movements; BSA, body surface area; CT, computed tomography; DKA, diabetic ketoacidosis; GAD, glutamic acid decarboxylase; immune checkpoint inhibitors, immune checkpoint inhibitors; ICU, intensive care unit; IV, intravenous; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; MRI, magnetic resonance imaging; N/A, not applicable; NSAIDs, nonsteroidal anti-inflammatory drugs; PFT, pulmonary function test; SJS, Steven-Johnson syndrome; TEN, toxic epidermal necrolysis; TRAb, thyroid-stimulating hormone receptor antibody; TSH, thyroid-stimulating hormone; ULN, upper limit of normal

Pancreatic toxicity associated with immune checkpoint inhibitor therapy is less common and usually presents as a transient increase in lipase or amylase. Acute pancreatitis is rare.[8,21,46,47] In the absence of symptoms, glucocorticoids are not needed,[8] but in symptomatic patients or in patients with severe elevation of pancreatic enzymes, other causes of pancreatitis need to be excluded, after which glucocorticoids may be needed.

3.3 | Neurologic immune-related adverse effects

Mild and nonspecific neurologic symptoms (eg, headaches, dizziness, and sensory impairment) have been reported in 6%–12% of patients, and severe (grade ≥3) neurologic immune-related adverse effects occur in <1% of patients treated with immune checkpoint inhibitors (Figures 4D and 4E).[16,48] immune checkpoint inhibitor-induced

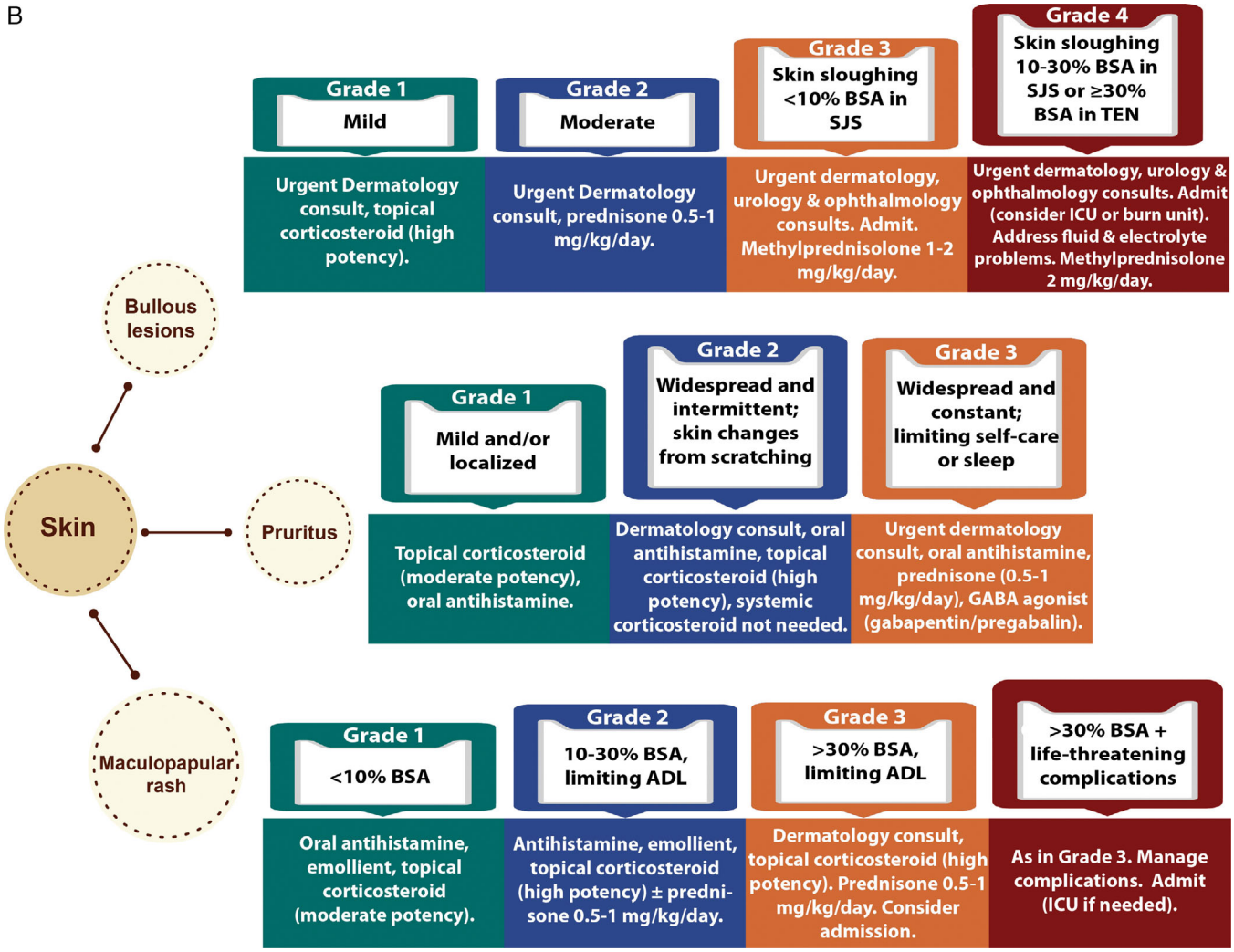


FIGURE 4 Continued

neurologic diseases include myasthenia gravis, Guillain-Barré syndrome, polyradiculoneuropathy, vasculitic neuropathies, isolated cranial neuropathies, aseptic meningitis, immune encephalitis, posterior reversible encephalopathy syndrome, myelopathy/transverse myelitis, Vogt-Harada-Koyanagi syndrome, neurosarcoidosis, and multiple sclerosis (demyelination). Most neurologic immune-related adverse effects occur within 3 months, with a median onset of 6 weeks. A useful framework for emergency physicians is to consider the main neurologic site of involvement: brain, spinal cord (myelopathy), peripheral nerve root, or neuromuscular junction.[49]

Immune encephalitis is a rare, but potentially fatal, immune-related adverse effect with an incidence of 0.1%–0.2%.[48,50–53] Severe symptoms include seizures, confusion, ataxia, aphasia, abnormal behavior, and altered consciousness. Emergency brain CT or magnetic resonance imaging (MRI) is indicated.[50,51,53] An electroencephalogram should be obtained if non-convulsive seizures are suspected. Peripheral smear can be used to exclude anemia or thrombotic thrombocytopenic purpura-related encephalopathy.[8] If other neurologic symptoms, including headache, photophobia, fever, and neck stiffness, are present with normal mental status, meningitis should be considered. The incidence of meningitis with ipilimumab is estimated to be around 0.1%–0.2%.[54] In the presence of meningeal signs and/or fever, analysis of cerebrospinal fluid, including polymerase chain reaction for herpes simplex virus and other viruses, cytology, oligoclonal bands, autoimmune encephalopathy, and paraneoplastic panels may be needed.[8,9,55] Other causes of the symptoms, such as infection, progression of cancer, and metabolic abnormalities, need to be excluded.[8] Management of suspected meningitis includes withholding immune checkpoint inhibitors, starting empirical antibiotics and acyclovir after cerebrospinal fluid analysis, and, for moderate to severe symptoms, starting glucocorticoids once bacterial and viral causes have been excluded.[8,9]

Immunotherapy-induced neuropathies are common in patients treated with immune checkpoint inhibitors. Symptoms including severe constipation, nausea, urinary problems, sexual difficulties, sweating abnormalities, sluggish pupil reaction, temperature dysregulation, and orthostatic hypotension are suggestive of autonomic neuropathy. Phrenic nerve palsy may lead to respiratory compromise.[8,9] For peripheral neuropathies, acute or chronic forms occur in ~3% of

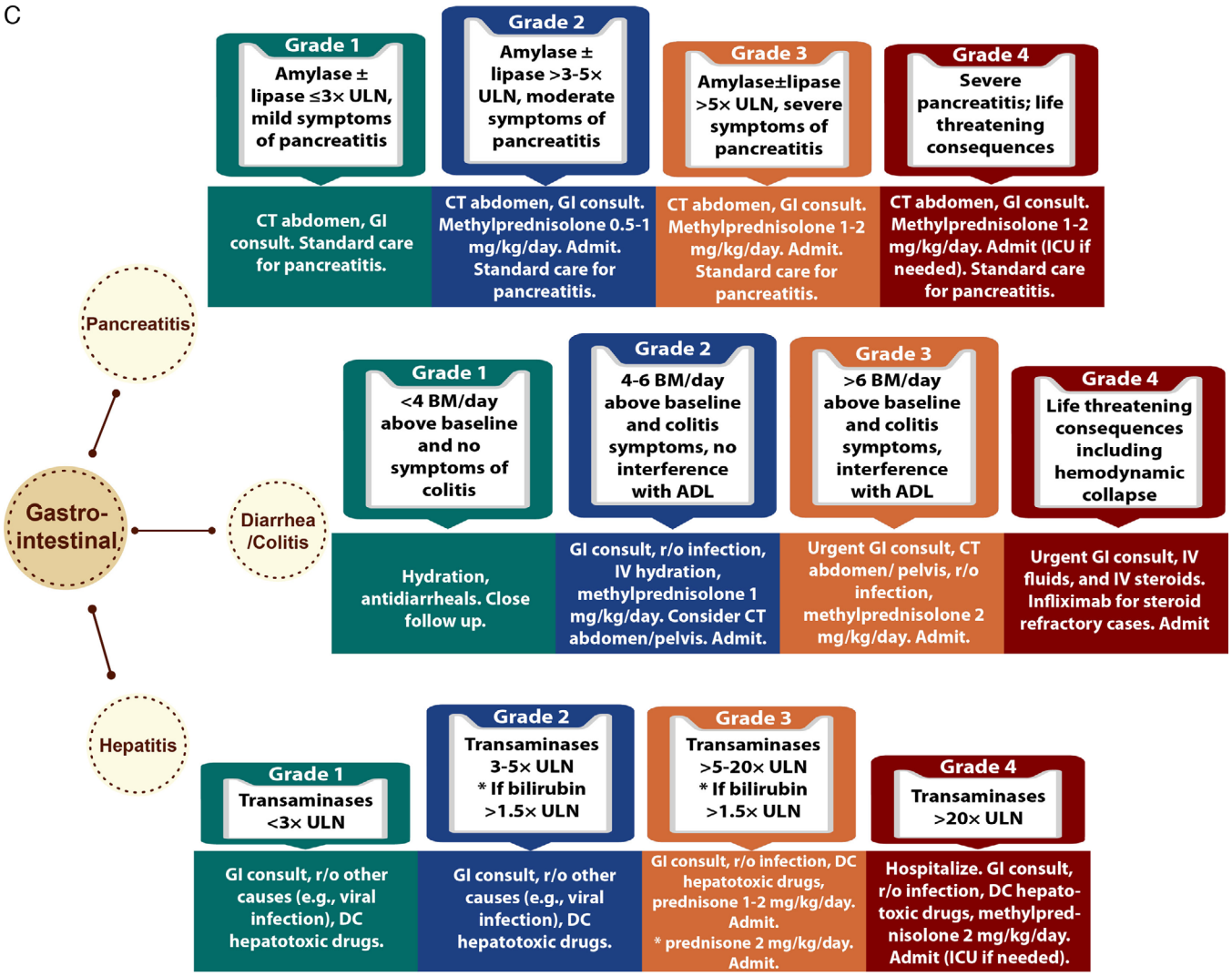


FIGURE 4 Continued

patients. In Guillain-Barré syndrome, recognizing respiratory muscle involvement is crucial because diaphragm paralysis results in the need for mechanical ventilation.[16,56] Bedside inspiratory force/vital capacity measurement, pulse oximetry, capnography, and arterial blood gas may aid in clinical decision making. Laboratory and imaging tests can help exclude other systemic causes of weakness.[8,16,21,56,57]

With a 30% mortality rate, and accompanied by respiratory compromise, myasthenia gravis is considered 1 of the most severe neurotoxicities associated with immune checkpoint inhibitors.[58–60] Other causes of the neurologic deficits may be ruled out with diagnostic imaging as directed by the symptoms. Confirmation would be done as an inpatient; from the ED, blood samples can be sent for analysis of anti-choline receptor antibodies, anti-muscle-specific-kinase antibodies, and anti-striational antibodies to assist the admitting team to confirm the diagnosis.[61] Management for grade 2 includes glucocorticoids (target dose of prednisone: 1 mg/kg/d) and pyridostigmine (30–120 mg 3 times daily), and for grades ≥3, monitoring and support ventilatory inadequacy (may need intensive care), intravenous methylprednisolone 1–2 mg/kg/d, and arrangements for plasmapheresis (or intravenous immunoglobulin in divided doses totaling 2 g/kg).[4] It is important to note that doses of methylprednisolone >2 mg/kg/d may paradoxically exacerbate the symptoms.

3.4 | Endocrine immune-related adverse effects

Patients with severe endocrinopathies can present to the ED with severe and life-threatening illness (eg, thyroid storm, myxedema coma, and diabetic ketoacidosis), and endocrine immune-related adverse effects in the ED are usually related to the thyroid, adrenal, and pituitary glands (Figure 4F).[7,62–65]

Hypophysitis (inflammation of the pituitary gland) has been most commonly associated with anti-CTLA-4 agents such as ipilimumab, followed by the combination of anti-CTLA-4 and anti-PD-1 agents (nivolumab). Hypophysitis has been rarely associated with single-agent anti-PD-1 or anti-PD-L1. Hypophysitis may lead to an adrenal

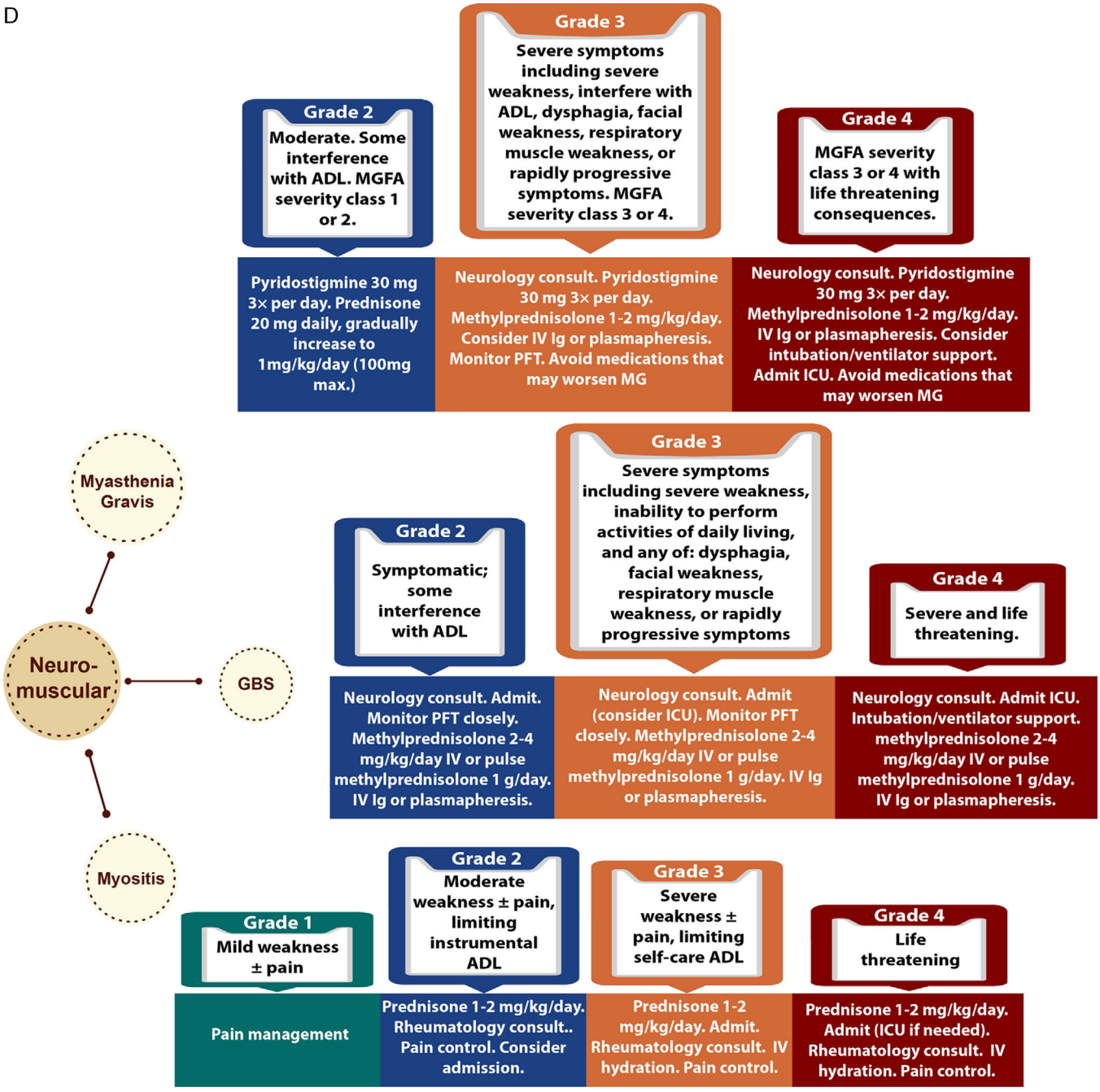
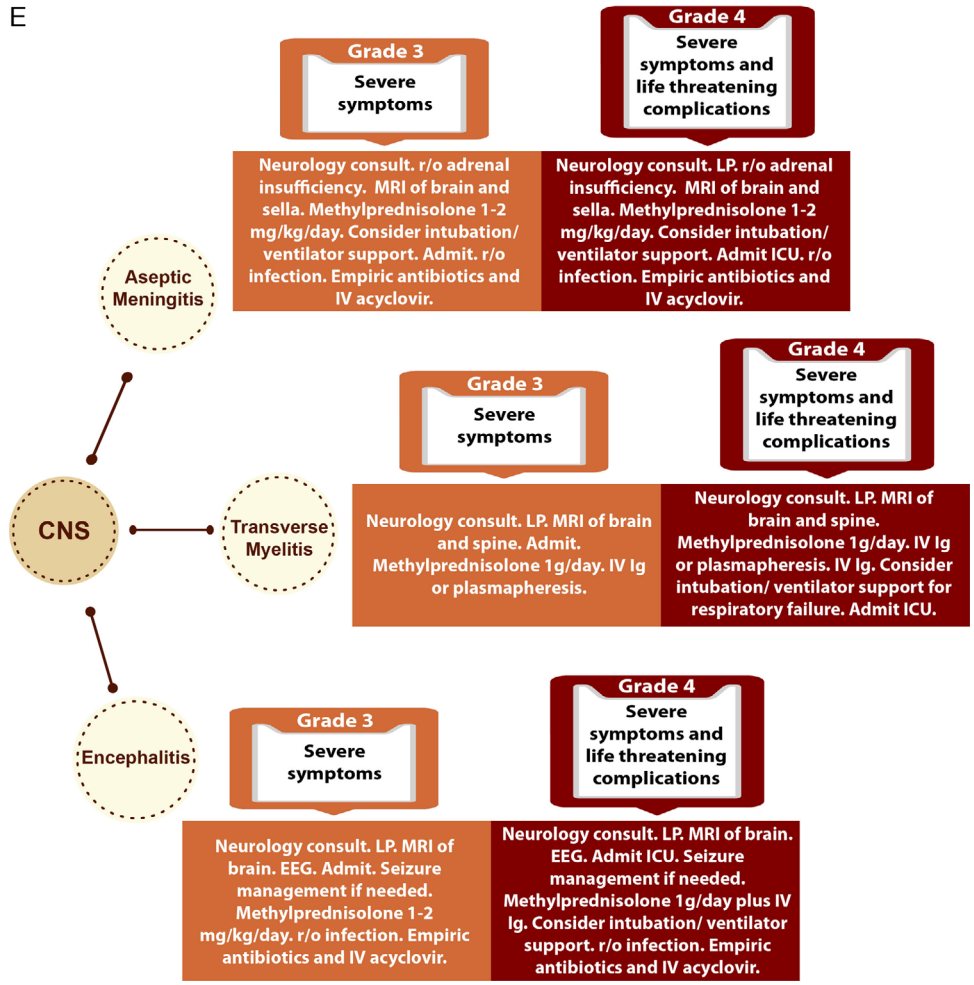


FIGURE 4 Continued

crisis.[66–68] Headache, fatigue, and general weakness are the dominant (89%) presenting symptoms in hypophysitis.[68] The symptoms are nonspecific and often misattributed to malignancy. Hyponatremia is present in ~50% of patients with hypophysitis.[68–70] The diagnosis requires brain/sella MRI, in which the pituitary gland may appear diffusely enlarged and homogeneously hyperintense on T_1-weighted post-contrast sequences. Acute morbidity and mortality from hypophysitis is mainly due to central adrenal insufficiency.[71] Initial treatment strategies include high-dose glucocorticoids in addition to management of hyponatremia and hypotension. In the absence of significant hyponatremia, severe headache, or pituitary enlargement that compresses the optic chiasm, physiologic replacement doses of glucocorticoids may be considered.[72]

Primary adrenal insufficiency as an immune-related adverse effect is uncommon but may be underreported.[73] Symptoms of adrenal crisis include hypotension, dehydration, and electrolyte abnormalities, which require immediate intervention in the ED.[71] A random cortisol level that is not appropriately increased in the presence of stress would corroborate a working diagnosis of adrenal insufficiency. These symptoms can improve rapidly after initiation of glucocorticoids.[68] The addition of fludrocortisone can optimize blood pressure and electrolytes.[74]



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Thyroid dysfunction can be primary (ie, thyroiditis or Graves' disease) or secondary (ie, hypophysitis with central hypothyroidism).[75] Thyroiditis typically has a clinical course of transient hyperthyroidism (due to release of thyroid hormones because of the destruction of the thyroid gland) followed by prolonged or permanent hypothyroidism.[75,76] Graves' disease is autoimmune hyperthyroidism due to stimulation by antibodies for thyroid-stimulating hormone receptor (thyrotropin receptor antibodies). Measurements of thyroid peroxidase antibodies and thyrotropin receptor antibodies can distinguish Graves' disease from thyroiditis. Thyrotoxicosis may precipitate arrhythmia, such as atrial fibrillation, flutter, and supraventricular tachycardia, leading to ED visits. The clinical presentation of thyrotoxicosis in thyroiditis is usually mild and manageable with β-blockers. However, in patients with Graves' disease, serious thyrotoxicosis may qualify as a thyroid storm that may require additional treatments (eg, anti-thyroid agents, glucocorticoids, potassium iodide, and iopanoic acid).[77,78] Fatigue is a very common nonspecific symptom of hypothyroidism.[79] However, unrecognized severe hypothyroidism may progress to myxedema coma. Severe hypothyroidism should be included in the differential diagnosis of immune checkpoint inhibitor-treated cancer patients presenting to the ED with confusion, lethargy, bradycardia, hyponatremia, or hypothermia. Management of hypothyroidism involves replacement of the thyroid hormone (levothyroxine) and supportive measures.[80]

Patients with new-onset type 1 diabetes mellitus may present with diabetic ketoacidosis after immune checkpoint inhibitor therapy.[81,82] The median onset time of immune checkpoint inhibitor-induced type 1 diabetes mellitus is 20 weeks after initiation of immune checkpoint inhibitor therapy,[83] but it can occur even after 1 dose.[12] Immune checkpoint inhibitor-induced type 1 diabetes mellitus occurs in middle-age and elderly adults rather than juveniles or young adults. Although immune checkpoint inhibitor-induced type 1 diabetes mellitus with diabetic ketoacidosis is rare, it is potentially fatal and requires early recognition. In addition to the classic symptoms of hyperglycemia (polyuria, polydipsia), tachypnea in respiratory compensation for severe metabolic acidosis can be a clinical clue. Bedside point-of-care chemistry, arterial blood gas analysis, and urine dipstick analysis for ketones allow rapid confirmation of diabetic ketoacidosis so that it can be treated in a timely manner with intravenous insulin infusion, intravenous fluid, and electrolytes.

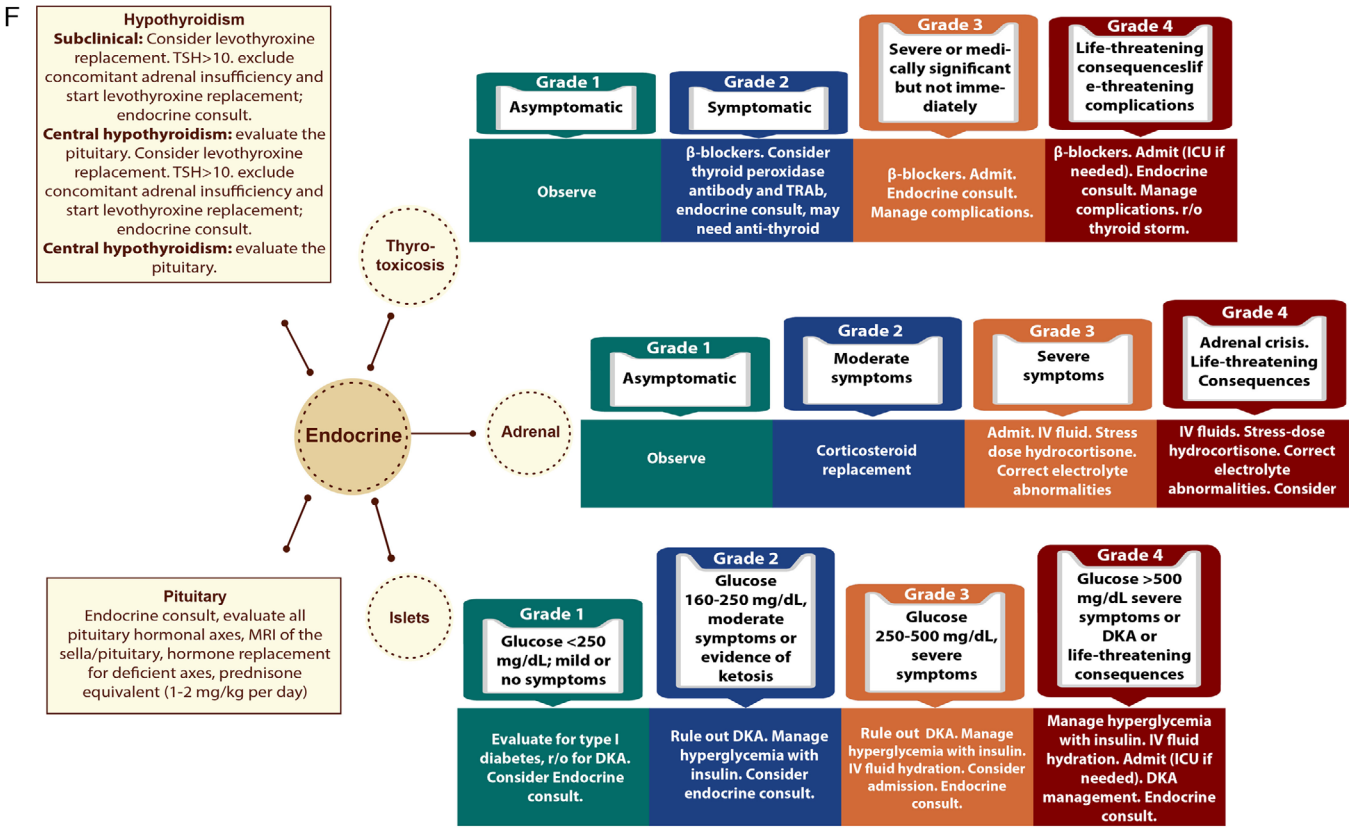


FIGURE 4 Continued

3.5 | Cardiac immune-related adverse effects

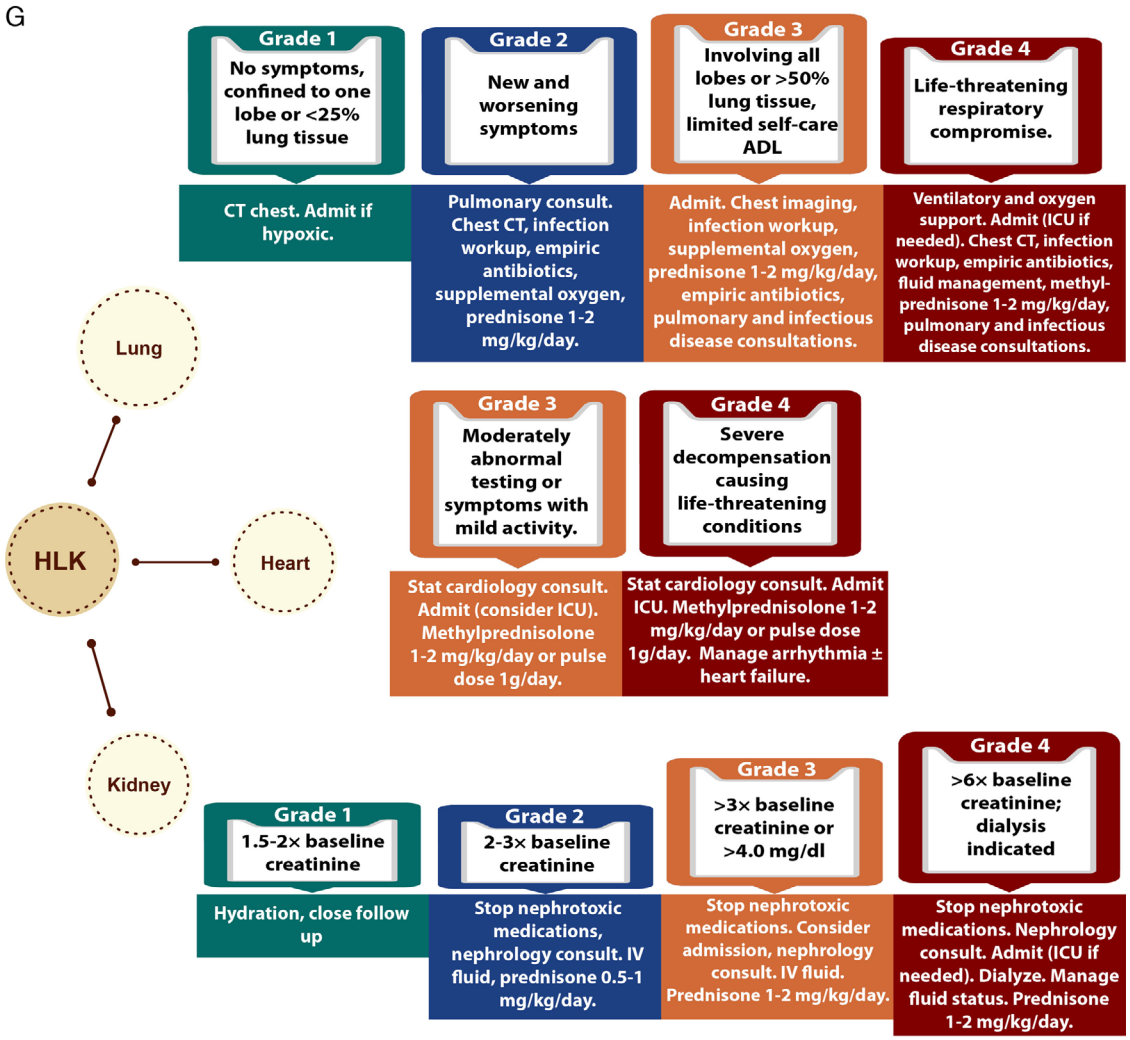
Patients with immune checkpoint inhibitor-induced lymphocytic infiltration of cardiac and pericardial tissue may present in the ED acutely with dyspnea, chest pain, fatigue, edema, palpitations, syncope, or even cardiac arrest (Figure 4G).[84–90] The reported incidence of cardiac immune-related adverse effects is around 1%.[84,85] Acute management of the cardiac complications should follow the Advanced Cardiac Life Support algorithms along with consideration for starting glucocorticoid therapy immediately. Presentation and treatment of immune checkpoint inhibitor-related acute coronary syndrome is similar to that of non-immune checkpoint inhibitor-related acute coronary syndrome, with the addition of stopping treatment with immune checkpoint inhibitors and starting treatment with high-dose steroids.[91,92]

Myocarditis is the most commonly cited cardiotoxicity related to immune checkpoint inhibitors.[93] Although most patients have elevated cardiac enzymes, some have been reported to have normal enzymes.[85] Endomyocardial biopsy is the gold standard for the diagnosis of myocarditis. The diagnosis of myocarditis can be confirmed with cardiac MRI, if the patient is unable to undergo cardiac biopsy.[8,10] The new proposed hierarchical definition of myocarditis that helps in the diagnosis of myocarditis in the setting of immune checkpoint inhibitors may also be used in the ED.[94] Up to 50% of patients diagnosed with myocarditis experience major adverse cardiac events that can poorly influence survival; patients with troponin T levels of ≥1.5 ng/mL are at increased (4-fold) risk of major adverse cardiac events.[10,85,95]

For pericarditis, the presenting symptoms, workup, and management are similar to that of myocarditis, and pericarditis is often associated with prior thoracic radiation.[91,96] Electrocardiogram (ECG) changes include PR depression and diffuse ST elevation; troponin may be elevated if the myocardium is involved, and evidence of pericardial inflammation might be visible on cardiac MRI or F^{13}-FDG positron emission tomography/CT.[91] Tamponade or restrictive physiology is assessed by echocardiography.

The arrhythmias most frequently encountered as cardiac immune-related adverse effects are atrial fibrillation, conduction abnormalities, ventricular fibrillation, and torsades.[97] Dysrhythmias are usually identified within 1 month of immunotherapy initiation. Overlapping presentation with other disorders, including myocarditis, vasculitis, and myositis, should prompt analysis of cardiac enzymes, ECG, and telemetry. Immediate management of dysrhythmias includes all standard cardiac interventions. For grade 3 and grade 4 toxicity, glucocorticoids should be started immediately once the diagnosis is suspected because this is one of the most fatal immune-related adverse effects.

Congestive heart failure is often associated with myocarditis and rarely presents alone. B-type natriuretic peptide and N-terminal pro B-type natriuretic peptide have high specificity and sensitivity, respectively, in diagnosing heart failure.[98] Along with high-dose corticosteroids that have been proven to be effective in treating immune checkpoint inhibitor-induced cardiotoxicities,[9] various pharmacologic agents can be used depending on the patient's clinical presentation for symptomatic relief, including diuretics (for edema),



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angiotensin-converting enzyme inhibitors, beta-adrenergic blockers, and aldosterone antagonists.[98]

Takotsubo cardiomyopathy has been reported in several cancer patients treated with immune checkpoint inhibitors.[99–101] Workup should include ECG, echocardiogram, B-type natriuretic peptide, and troponin. Further testing such as coronary angiography may demonstrate unobstructed coronary arteries, and myocarditis as a cause of ventricular impairment should be ruled out.[91] Heart failure can be managed using the management algorithm of the Heart Failure Association, and QT-prolonging agents should be avoided. If cardiogenic shock is predicted, then inotropic support and advanced mechanical support may be indicated.

3.6 | Rheumatologic immune-related adverse effects

Rheumatic and musculoskeletal immune-related adverse effects of immune checkpoint inhibitors include arthralgia and inflammatory arthritis, sicca symptoms, polymyalgia-like syndrome, and myositis.[15,102]

Myositis presents as proximal muscle weakness with elevated serum muscle enzymes, with or without respiratory complaints,[85,103–116] and symptom onset usually occurs within the first 2 months after treatment with immune checkpoint inhibitors.[117,119] Shortness of breath can occur owing to respiratory muscle weakness or congestive heart failure due to concurrent immune-related myocarditis.[54,118,120,121] Although it is rare (<1%), immune checkpoint inhibitor-induced myositis has a high reported fatality rate (5%–13%),[120,122,123] as a consequence of ventilation failure, renal failure due to severe rhabdomyolysis, electrolyte imbalance, or fatal arrhythmias. Concurrent myocarditis develops in 20%–40% of cases, worsening the prognosis.[58,117,119,120,124] Concomitant myasthenia-like manifestations may also occur.[103,113] On suspicion of immune-related adverse effect myositis, creatine kinase and aldolase analysis should be performed. Troponin analysis and ECG can also be performed to identify myocardial involvement.[58,117,119,120,124] If ventilation is compromised, evaluation with peak flows, bedside pulmonary

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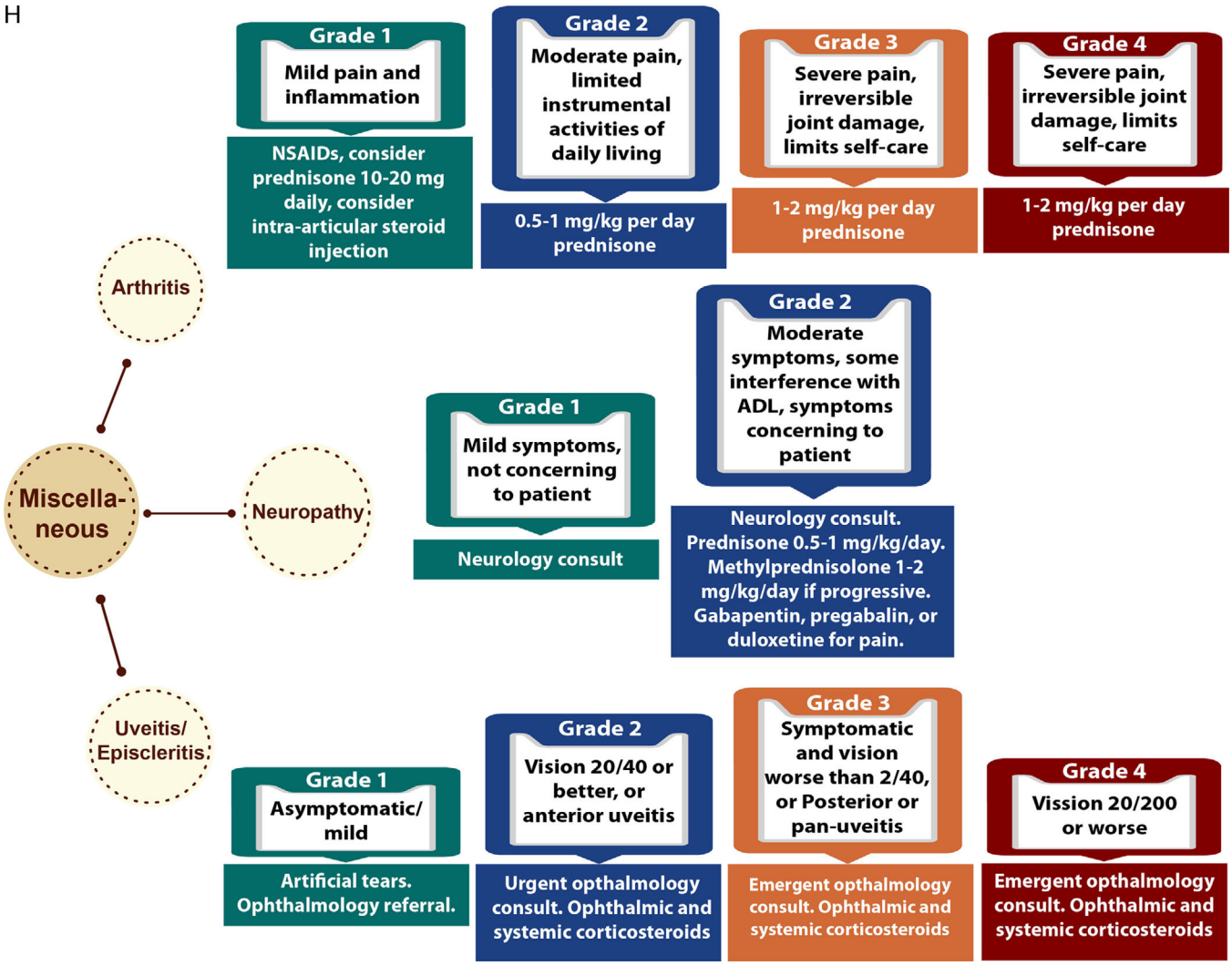

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function tests, and arterial blood gas measurement is required because the patient may need positive pressure ventilation or intubation for ventilation.[119,120,122] Other specialized diagnostic workup may be used in coordination with specialists.[54,117,119–122,125,126] For grade 1 myositis, monitoring creatine kinase/aldolase levels and treating pain is adequate.[4,8] For grade ≥2 myositis, starting corticosteroids and withholding immune checkpoint inhibitor therapy is needed.[4,8] In severe (grade ≥3) or refractory cases (ie, patients presenting to the ED with already diagnosed immune-related adverse effect myositis but not responding to glucocorticoid therapy), serial monitoring of aldolase/creatine kinase and discussion with oncologists and neurology or rheumatology consultants for further management will be needed.

Arthritis/arthralgia is usually underreported but its incidence ranges from 5%–16%, with higher rates in patients who have received combination immune checkpoint inhibitor therapy (Figure 4H).[121,127–130] Presentation can be a spectrum of forms, including polyarthritis resembling rheumatoid arthritis or spondyloarthritis. Forms resembling reactive arthritis, polymyalgia rheumatica, and psoriatic arthritis have also been reported.[121,128,129] In the ED, septic arthritis,[131,132] metastatic disease, and pathologic fractures need to be ruled out.[8,9,129,133] Acetaminophen or nonsteroidal anti-inflammatory drugs are sufficient for patients with grade 1 arthritis. Grade ≥2 arthritis warrants treatment with glucocorticoids. For patients with grade 3–4 arthritis with severe pain, irreversible joint damage, and limitations of self-care,[4,8,9,21,129] management includes permanently discontinuing immune checkpoint inhibitors and referring the patient to a rheumatologist for further management.

Sarcoid-like reactions have been associated with immune checkpoint inhibitor therapy.[134–136] Asymptomatic patients do not require therapy unless they have radiologic evidence of extensive disease.[137–139] Most symptomatic patients (ie, those with fever, chest pain, dyspnea, or weight loss) find that their symptoms improve with immune checkpoint inhibitor discontinuation, but corticosteroids can be used in refractory cases.[134,137,140]

3.7 | Pulmonary immune-related adverse effects

As with other organ systems, pulmonary toxicities of immune checkpoint inhibitor therapy are diverse. Although pneumonitis is the most feared pneumotoxicity,[141] others include sarcoid-like granulomatous reactions and pleural effusion.[135,142] Clearly, we have not yet catalogued the full scope of toxicities. In general, CTLA-4 inhibiters have higher incidence of pulmonary immune-related adverse effects than do PD-1/PD-L1 inhibitors.[143] This is reflected in a higher incidence of treatment-related mortality.[144] Pulmonary immune-related adverse effects often present as dyspnea and nonproductive cough, and less commonly as chest pain.[30,145] New persistent cough or shortness of breath in patients receiving immune checkpoint inhibitors should prompt evaluation for pneumonitis. The incidence of pneumonitis is 3%–5%,[145–148] with higher incidence among patients treated with PD-1 and PD-L1 inhibitors compared with those receiving CTLA-4 therapy, and pneumonitis usually occurs within 3 months of immune checkpoint inhibitor treatment initiation.

Immune checkpoint inhibitor-induced pneumonitis may progress to acute respiratory distress syndrome or respiratory failure, which can be fatal.[71,145,149–151] In patients with acute presentation of pneumonitis, infectious pneumonia is in the differential diagnosis, and empiric antibiotics coverage is indicated. Close observation is sufficient for patients with grade 1 pneumonitis. Grade ≥2 pneumonitis warrants glucocorticoids.[8] Grade ≥3 pneumonitis requires inpatient care, evaluation to exclude infections, pulmonary and infectious disease consultations, and high-dose glucocorticoids after discussion with the oncologist. If necessary, intubation or tracheostomy can be used to secure the airways, along with standard supportive care. Other immunosuppressive agents (eg, infliximab, mycophenolate mofetil) or intravenous immunoglobulins are generally not used in the ED but may be used after admission if no clinical improvement occurs within 48 hours. Pneumonitis flare has been reported after the steroid regimen and typically responds to repeated steroid administration.[145]

3.8 | Hematologic immune-related adverse effects

Pancytopenia (immune aplastic anemia), isolated neutropenia, hemolytic anemia, and idiopathic TTP (immune thrombocytopenia) are immune-related adverse effects.[24] Treatment in the ED may involve transfusion support, management of neutropenic fever, and management of acute bleeding complications related to severe thrombocytopenia. Bleeding risk for immune thrombocytopenia may be assessed using a bleeding score by Khellaf et al.[152] A high score (>8) indicates that immediate treatment is needed with intravenous immunoglobulins in combination with glucocorticoids.[24] Review of the cancer treatment history in the ED is extremely important because cytopenia in the absence of recent cytotoxic chemotherapy or radiation or to an unexpected extent given the chronology of exposure to chemotherapy or radiation should raise suspicion for immune cytopenia, and glucocorticoid therapy should be considered in consultation with the oncologist.

Hemophagocytic lymphohistiocytosis, also known as macrophage activation syndrome, is characterized by hyper-inflammation and progressive immune-mediated organ damage. Hemophagocytic lymphohistiocytosis due to immune checkpoint inhibitors is rare but potentially fatal. Its diagnosis is based on having at least 5 of the following criteria: (1) fever, (2) cytopenias (at least 2 lineages in complete blood counts), (3) splenomegaly, (4) hypertriglyceridemia or hypofibrinogenemia, (5) high serum ferritin, (6) hemophagocytosis, (7) low natural killer cell function, and (8) high soluble interleukin-2.[153,154] Some of the diagnostic criteria often cannot be assessed in the ED, but hemophagocytic lymphohistiocytosis should be considered in the differential diagnosis for cancer patients treated with immune checkpoint inhibitors who present to the ED with fever, cytopenias, and splenomegaly.[155] Morbidity and mortality due to hemophagocytic lymphohistiocytosis are partially due to delayed diagnosis, and a high index of suspicion should facilitate early intervention with high-dose glucocorticoids.

3.9 | Renal immune-related adverse effects

The incidence of renal immune-related adverse effects following immunotherapy is <2% with single-agent immune checkpoint inhibitor therapy and ~ 4%–5% with combination therapy (ipilimumab and nivolumab).[156,157] Although onset of renal immune-related adverse effects following treatment with PD-1/PD-L1 inhibitors can occur 3–10 months after treatment, renal immune-related adverse effects tend to occur earlier (<3 months) in patients receiving anti-CTLA-4 agents.[156] Elevated creatinine levels are uncommon (0%–4%) and acute kidney injury is rare.[158] Two varied forms of immunotherapy-induced renal parenchymal damage have been reported: acute tubulointerstitial nephritis and immune complex glomerulonephritis.[158] Most patients with renal immune-related adverse effects tend to be asymptomatic despite having elevated creatinine levels. Once symptoms emerge, these may include decreased urine output, hematuria, and edema.[156] If renal immune-related adverse effects are suspected, imaging studies to rule out obstructive causes may be needed, along with a renal biopsy to confirm the diagnosis.[156]

The mainstay of treatment for renal immune-related adverse effects is glucocorticoid therapy.[156] For grade 1 renal immune-related adverse effects, strict monitoring of creatinine levels, promoting hydration, and discontinuation of all nephrotoxic agents (eg, contrast agents) is important.[158] For grades 2 and 3 renal immune-related adverse effects, immune checkpoint inhibitors should be suspended until creatinine levels return to normal and the patient's condition has improved.[156,158] For grade 4 renal immune-related adverse effects, immunotherapy should be stopped. A renal biopsy helps assess the underlying renal damage. Alternative immunosuppressive regimens should be considered in cases when glucocorticoid therapy fails.[158]

3.10 | Ophthalmologic immune-related adverse effects

Although uncommon (<1% of patients), ophthalmologic immune-related adverse effects can present as serious adverse events, resulting in poor quality of life and discontinuation of immune checkpoint inhibitors.[159] These events typically occur within weeks to months of immunotherapy initiation[5,13,160,161] and present as blurred or double vision, change in color vision, photophobia, visual distortion, scotomas, floaters, visual field changes, tenderness, pain with eye movement, eyelid swelling, or proptosis.[8,21,161] Ophthalmologic immune-related adverse effects are often seen in conjunction with other organ toxicities, specifically colitis, and they include uveitis, episcleritis, blepharitis, peripheral ulcerative keratitis, thyroid-associated or idiopathic orbital inflammation, retinal and choroidal diseases, and optic neuropathies.[8,13,21,160] After a comprehensive ophthalmic examination, treatment of these rare immune-related adverse effects depends on their severity. After infectious conditions (eg, herpetic keratitis/uveitis) have been ruled out, mild ophthalmologic immune-related adverse effects can be treated with observation alone or topical and periocular glucocorticoids. Systemic corticosteroids and immunosuppressants are reserved for more severe ocular and orbital inflammation.[8,160] Cessation of immune checkpoint inhibitor therapy can be required in severe treatment-refractory or recurrent cases.[8,29]

4 | PEARLS AND POTENTIAL PITFALLS

- For dermatological immune-related adverse effects, watch out for bullous lesions, Niklosky sign and mucosal involvement.
- Multiple immune-related adverse effects may occur concurrently. When 1 immune-related adverse effect is diagnosed, be alert for signs and symptoms that may suggest other immune-related adverse effects. In particular, myositis, myocarditis, and myasthenia gravis may present concurrently.
- Beware of diabetic ketoacidosis in patients with hyperglycemia. In diabetic patients who are on SGLT2 inhibitors, beware of euglycemic diabetic ketoacidosis.
- Consider abdominal imaging studies such as CT scan of abdomen for severe diarrhea, especially with abdominal pain. Consider infectious causes along with immune-related adverse effects in the differential diagnosis and management.
- In patients with dyspnea or mental status, arterial blood gases is informative in the differential diagnosis of pneumonitis, pulmonary edema (congestive heart failure from myocarditis), and ventilatory failure (myositis, myasthenia gravis, or Guillain-Barre syndrome).
- Hyponatremia should raise suspicion of hypoadrenalism and/or hypothyroidism (ie, adrenalitis, thyroiditis, or hypophysitis).
- In the presence of severe fatigue and/or hypotension, adrenal insufficiency must be excluded.
- Discuss with the primary oncologist when initiating steroid therapy for newly diagnosed immune-related adverse effect or second-line therapy for immune-related adverse effect that is not responding to steroid therapy.
- Beware of thrombotic TTP in thrombocytopenic patients; a helpful mnemonic is fever, anemia, thrombocytopenia, renal failure, and neurological symptoms (FAT RN). Keep in mind that sepsis may also be in the differential diagnosis.
- In patients with severe sepsis or systemic inflammatory response syndrome (SIRS) or significant elevation of liver function tests, consider the possibility of HLH.

5 | CONCLUSION

In summary, immune checkpoint inhibitors are associated with a constellation of toxicities known as immune-related adverse effects.[156] Some immune-related adverse effects that are mild can be treated in an outpatient setting, whereas others are severe enough to present as urgent/emergent cases in the ED. Proper diagnosis and management of immune-related adverse effects presenting in the ED can influence patient outcomes and reduce both morbidity and mortality rates associated with these events. We have reviewed the current guidelines and reports related to immune-related adverse effects and provided a comprehensive overview of immune-related adverse effects that can present in the ED. We have also summarized our approach to diagnose and manage immune-related adverse effects in the ED. With the wide spectrum of immune-related adverse effects, some of which can be life-threatening, quick recognition and appropriate management will likely improve patient outcomes. Our colleague, Dr. Aung Naing, worked with app developers and has created an app (IO TOX) to provide a quick reference for oncologists and emergency department clinicians. This free app can be downloaded at https://apps.apple.com/us/app/io-tox-management/id1514006592?ls=1 for iPhone/iPad or https://play.google.com/store/apps/details?id=com.projectronin.iotoxman for Android devices.

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CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

S.C.J.Y., P.B., C.R.-G., and K.A. developed the article concept and provided administrative support. S.-C.J.Y. drafted the first version of the article. S.C.J.Y. performed the computer literature search and word mining. S.C.J.Y., A.Q., P.C., D.L., J.M., E.R., A.W., M.S., J.V., A.A.-B., M.S., R.P., M.K., O.K., K.T., M.W., A.E., S.G., and P.B. were responsible for

content analysis. S.C.J.Y., A.Q., E.R., and A.A.B. created the figures and tables. All authors assisted in drafting the article, made critical revisions for important intellectual content, and approved the final version of the article. S.C.J.Y. takes final responsibility for the paper as a whole.

ORCID

Sai-Ching Jim Yeung MD, PhD https://orcid.org/0000-0001-5170-0822

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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APPENDIX

Figure 4 in poster format (pdf).