Management of Immunotherapy-Related Toxicities, Version 1.2019

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ABSTRACT

The aim of the NCCN Guidelines for Management of Immunotherapy-Related Toxicities is to provide guidance on the management of immune-related adverse events resulting from cancer immunotherapy. The NCCN Management of Immunotherapy-Related Toxicities Panel is an interdisciplinary group of representatives from NCCN Member Institutions and ASCO, consisting of medical and hematologic oncologists with expertise in a wide array of disease sites, and experts from the fields of dermatology, gastroenterology, neuro-oncology, nephrology, emergency medicine, cardiology, oncology nursing, and patient advocacy. Several panel representatives are members of the Society for Immunotherapy of Cancer (SITC). The initial version of the NCCN Guidelines was designed in general alignment with recommendations published by ASCO and SITC. The content featured in this issue is an excerpt of the recommendations for managing toxicity related to immune checkpoint blockade and a review of existing evidence. For the full version of the NCCN Guidelines, including recommendations for managing toxicities related to chimeric antigen receptor T-cell therapy, visit NCCN.org.

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NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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The complete NCCN Guidelines for Management of Immunotherapy-Related Toxicities are not printed in this issue of *JNCCN* but can be accessed online at NCCN.org.

Disclosures for the NCCN Management of Immunotherapy-Related Toxicities Panel

At the beginning of each NCCN Guidelines Panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Management of Immunotherapy-Related Toxicities Panel members can be found on page 289. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

The complete and most recent version of these guidelines is available free of charge at NCCN.org.

Overview

The aim of the NCCN Guidelines for Management of Immunotherapy-Related Toxicities is to provide guidance on the management of immune-related adverse events (irAEs) resulting from cancer immunotherapy. The NCCN Management of Immunotherapy-Related Toxicities Panel is an interdisciplinary group of representatives from NCCN Member Institutions and ASCO. The panel consists of medical oncologists and hematologic oncologists with expertise in a wide array of disease sites, as well as experts from the fields of dermatology, gastroenterology, neurooncology, nephrology, emergency medicine, cardiology, oncology nursing, and patient advocacy. Several NCCN Panel representatives are members of the Society for Immunotherapy of Cancer (SITC). The initial version of the NCCN Guidelines was designed in general alignment with recommendations published by ASCO and SITC.[1,2]

The content featured in this issue is an excerpt of the recommendations for managing toxicity related to immune checkpoint blockade and a review of existing evidence. For the full version of these NCCN Guidelines, including recommendations for managing toxicities related to chimeric antigen receptor (CAR) T-cell therapy, please see NCCN.org.

Immune Checkpoint Inhibitors

Some of the most effective immunotherapies to date target immune checkpoints exploited by cancers to decrease immune activity. This section discusses what is known regarding immune checkpoint inhibitor (ICI)-mediated immune dysfunction. For a discussion of the efficacy data for ICIs, see the NCCN Guidelines for treatment of cancer by site at NCCN.org.

ICI-Mediated Immune Dysfunction

The pharmacodynamics and pharmacokinetics of ICI immunotherapy differ greatly from that of cytotoxic chemotherapy or targeted anticancer therapy.[3] Similarly, anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and anti-PD-1/PD-L1 immunotherapies are associated with toxicity profiles that are distinct from those sen with conventional anticancer therapies, though their presentation may at times be similar.[4–10] Whereas traditional cytotoxic chemotherapy often results in acute-onset emetic and myelosuppressive effects, irAEs tend to have a relatively delayed onset and be inflammatory or autoimmune in nature.[11–14]

Although the pathophysiology of ICI-related irAEs is not yet fully elucidated, knowledge regarding the role of immune checkpoint pathways in autoimmune disease provides some clues. Many autoimmune diseases are related to failure of T-cell tolerance and uncontrolled activation of immune effector cells. Alterations in the genes encoding immune checkpoint proteins have been implicated in autoimmune disease. CTLA-4 and PD-1 polymorphisms have been linked to human autoimmune diseases including celiac disease, diabetes mellitus, lupus, rheumatoid arthritis, and autoimmune thyroid disease. The spectrum of irAEs associated with blockade of immune checkpoints falls in line with the phenotypes seen as a result of mutations in the genes encoding CTLA-4 and PD-1 and has considerable overlap across the various ICIs.[15–18]

The precise pathophysiology of ICI-mediated irAEs is currently unknown. Translational research provides some evidence that irAEs may result from some combination of autoreactive T cells, autoantibodies, and/or proinflammatory cytokines (eg, interleukin [IL]-17).[17,19] One potential mechanism is T-cell activity directed at antigens present in both tumor cells and healthy tissue.[20,21] Inflammation in otherwise normal tissues could result from elevated levels of inflammatory cytokines as a downstream effect of T-cell activation.[22–25] Additionally, direct binding of immune checkpoint antibodies to targets expressed in normal tissues (eg, CTLA expression in the pituitary) could lead to complement-mediated inflammation.[26,27] Finally, immunotherapy might increase the levels of pre-existing autoreactive antibodies.[28]

Early- and later-onset irAEs may result from distinct mechanisms that have yet to be elucidated. Typical earlier-onset, common irAEs appear to involve generalized epithelial inflammation and may be observed in the form of rash, colitis, and pneumonitis. These irAEs typically involve recruitment of neutrophils into normal tissues. Later-onset irAEs, which are typically less common, can include neurologic events and hypophysitis, among others. These tend to be more localized, organ-specific reactions. Research is ongoing into the specific mechanisms underlying irAEs associated with specific ICIs.

Incidence and Prevalence of irAEs

The incidence and prevalence of ICI-related toxicity is still being fully elucidated; many of the existing figures are based on trials of ipilimumab, pembrolizumab, and nivolumab. Comprehensive irAE data on newer agents are still being collected and analyzed. Due to the nature of irAEs and inconsistent reporting, it is likely that reported rates underestimate the actual incidence of these events. The reported incidence of any-grade irAEs associated with single-agent ICI treatment ranges widely across agents and trials, from approximately 15% to 90%.[1,29] Severe irAEs requiring immunosuppression and hold or discontinuation of treatment are estimated between 0.5% and 13% for monotherapy.[29] Analysis of pooled trial data found that 43% of patients discontinued

PRINCIPLES OF ROUTINE MONITORING

Baseline Assessment[a]	Monitoring Frequency[b]	Evaluation for Abnormal Findings/Symptoms
Clinical • Physical examination • Comprehensive patient history of any autoimmune/organ-specific disease, endocrinopathy, or infectious disease • Neurologic examination • Bowel habits (typical frequency/consistency)	Clinical exam at each visit with adverse event (AE) symptom assessment	Follow-up testing based on findings, symptoms
Imaging • CT imaging • Brain MRI if indicated	Periodic imaging as indicated	Follow-up testing as indicated based on imaging findings
General bloodwork • CBC with differential • Comprehensive metabolic panel • Infectious disease screening as indicated	Repeat every 2–3 weeks during immunotherapy, then in 6–12 weeks or as indicated	HbA1c for elevated glucose
Dermatologic (ICI_DERM-1) • Examination of skin and mucosa if history of immune-related skin disorder	Conduct/repeat as needed based on symptoms	Monitor affected BSA and lesion type; photographic documentation. Skin biopsy if indicated.
Pancreatic (ICI_ENDO-1) • Baseline testing is not required.	No routine monitoring needed if asymptomatic	Amylase, lipase, and consider abdominal imaging for suspected pancreatitis.
Thyroid (ICI_ENDO-2) • Thyroid-stimulating hormone (TSH), free thyroxine (T4)	Every 4–6 weeks during immunotherapy, then follow-up every 12 weeks as indicated	Total T3 if abnormal thyroid function suspected. TPO antibodies if TSH is high, TRAbs if TSH is low.
Adrenal/Pituitary (ICI_ENDO-3) • Adrenal: Serum cortisol • Pituitary: TSH, free T4	Every 2–3 weeks during immunotherapy, then follow-up every 6–12 weeks	Luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, adrenocorticotropic hormone (ACTH)
Pulmonary (ICI_PULM-1) • Oxygen saturation (resting and with ambulation) • Pulmonary function tests (PFTs) for high-risk patients	Repeat oxygen saturation tests based on symptoms	Chest CT to evaluate for pneumonitis, biopsy if needed to exclude other causes.
Cardiovascular (ICI_CARDIO-1) • Individualized assessment in consultation with cardiology as indicated	Consider periodic testing for those with abnormal baseline or symptoms	Individualized follow-up in consultation with cardiology as indicated
Musculoskeletal (ICI_MS-1) • Joint examination/functional assessment as needed for patients with pre–existing disease	No routine monitoring needed if asymptomatic	Consider rheumatology referral.

[a] Prior to initiating treatment, counsel patients on the warning signs and symptoms of immune-related adverse events (irAEs).
[b] Closer monitoring may be required for patients with combination immunotherapy regimens. Refer to prescribing information for each individual immuntherapy agent for monitoring recommendations.

combination therapy (nivolumab/ipilimumab) due to AEs, with gastrointestinal (GI) events being the most commonly reported reason for discontinuation.[30] ICI immunotherapies have been associated with rare AEs that are still being identified and studied at high-volume centers.

Single-Agent Therapy

CTLA-4

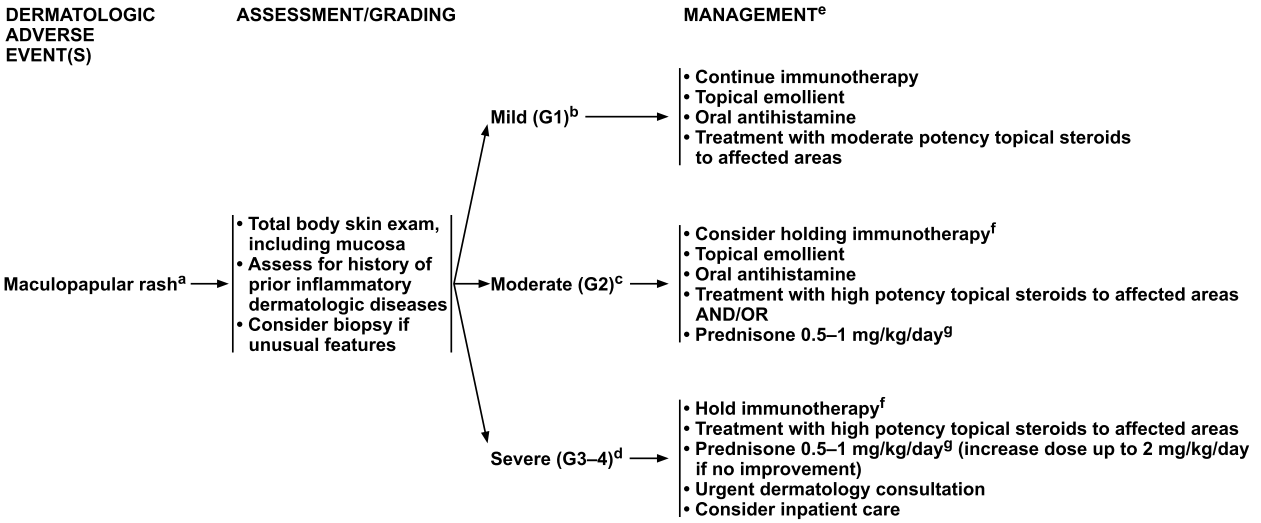
A 2015 meta-analysis by Bertrand et al[31] examined data from 1,265 patients across 22 clinical trials of anti–CTLA-4 antibodies (ipilimumab [n=1,132] and tremelimumab [n=133]), reporting an overall incidence of 72% for any-grade irAEs and 24% for high-grade irAEs. The most commonly observed AEs were dermatologic and GI, followed by endocrine and hepatic events. A randomized, double-blind, phase III trial in patients with unresectable or metastatic melanoma revealed a dose-dependent effect in treatment-related AEs for patients receiving ipilimumab at a dose of 3 mg/kg (n=362) or 10 mg/kg (n=364).[32] High-grade irAEs were reported in 18% and 30% of the 3 mg/kg and 10 mg/kg treatment groups, with 2 and 4 treatment-related deaths, respectively. The most common high-grade AEs, including diarrhea, colitis, elevated liver enzymes, and hypophysitis, were all more common at the higher dose of ipilimumab.[32] Adjuvant use of ipilimumab (10 mg/kg) for resected stage III melanoma appears to be associated with a higher incidence of AEs. Based on phase III data in patients receiving adjuvant ipilimumab (n=475), the incidence of high-grade irAEs was 41.6% with 5 fatalities (1.1%).[33,34]

PD-1/PD-L1

For PD-1/PD-L1 inhibitors, the reported overall incidence of any-grade irAE was up to 30% based on patients in phase III trials.[1,35–37] To date, the incidence of high-grade AEs associated with PD-1/PD-L1 inhibitors appears to be somewhat less dose-dependent than for ipilimumab and to vary by disease site.[29] In a recent meta-analysis of anti-PD-1/PD-L1 agents, any-grade and severe-grade irAEs occurred in about 26.8% and 6.1% of patients, respectively.[38] Rates of high-grade irAEs were similar across pembrolizumab, nivolumab, and atezolizumab, ranging from 5% to 8%.[38]

De Velasco et al[39] recently reported on the incidence of the most common ICI-associated irAEs in a meta-analysis of 21 randomized phase II/III trials conducted

Dermatologic Toxicity



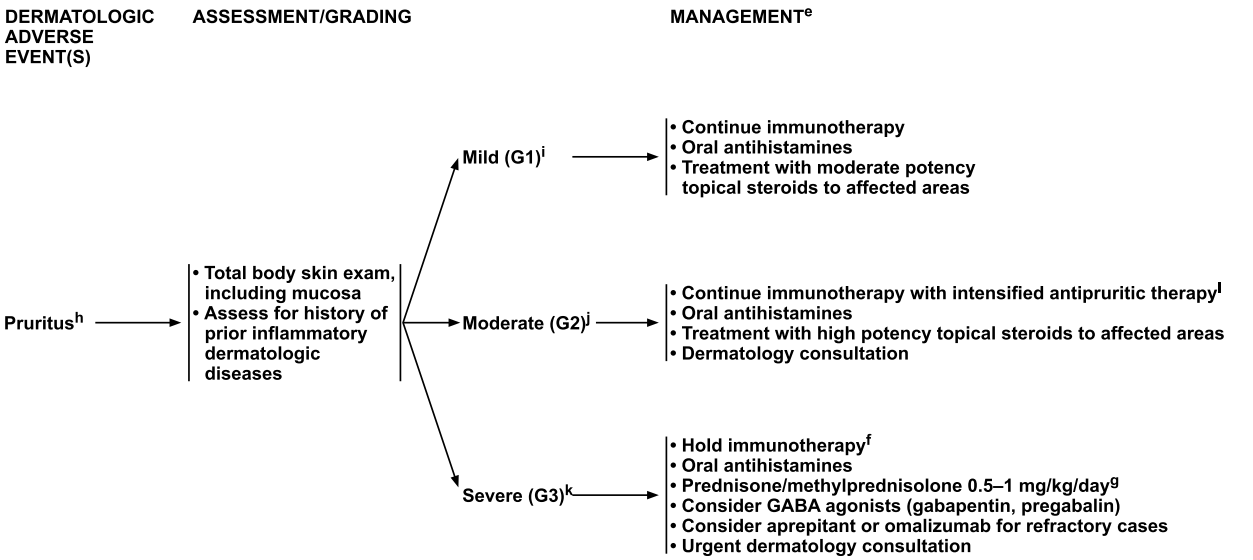
[a] Characterized by the presence of macules (flat) and papules (elevated). Also known as morbilliform rash, it is one of the most common cutaneous adverse events (AEs), frequently affecting the upper trunk, spreading centripetally and may be associated with pruritus.
[b] Macules/papules covering <10% body surface area (BSA) with or without symptoms (eg, pruritus, burning, tightness).
[c] Macules/papules covering 10%–30% BSA with or without symptoms (eg, pruritus, burning, tightness); limiting instrumental activities of daily living (iADLs).
[d] Macules/papules covering >30% BSA with or without associated symptoms; limiting self-care activities of daily living (ADLs).
[e] See Principles of Immunosuppression (IMMUNO-A, available online, in these guidelines, at NCCN.org).
[f] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[g] Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.

ICI_DERM-1

from 1996 to 2016. The trials included a total of 6,528 patients who received monotherapy (atezolizumab, n=751; ipilimumab, n=721; nivolumab, n=1,534; pembrolizumab, n=1,522) and 4,926 patients in placebo or standard therapy control arms using chemotherapy or biologic agents.[39] Due to inconsistent recognition and reporting of less-common irAEs in the clinical trial data, this meta-analysis was limited to examination of 5 common and well-documented types of irAEs: colitis, liver toxicity (aspartate transaminase [AST] elevation), rash, hypothyroidism, and pneumonitis. When compared with patients in trial control arms, patients receiving ICIs were found to be at greater risk for any-grade immune-related colitis, AST elevation, rash, hypothyroidism, and pneumonitis. Within this cohort, across all ICIs, the incidence of grade 3/4 events was 1.5% for colitis, 1.5% for liver toxicity, 1.1% for rash, 0.3% for hypothyroidism, and 1.1% for pneumonitis. High-grade colitis and rash were significantly more common among patients on ipilimumab than in those receiving PD-1/PD-L1 inhibitor.[39] In a separate review of the data, Kumar et al [29] also compared the risk of developing certain irAEs with different classes of ICIs. Although ipilimumab was associated with higher rates of colitis, pruritus, rash, and hypophysitis, PD-1/PD-L1 inhibitors resulted in a higher risk for developing vitiligo (typically observed in patients with melanoma), thyroid dysfunction, hepatotoxicity, and pneumonitis.[29]

De Velasco et al[39] compared the risk of developing specific irAEs by tumor type (melanoma, lung, and other), reporting no significant differences for all-grade or high-grade irAEs. Khoja et al[40] also conducted a systematic review of irAEs by ICI class and tumor type in 6,869 patients in 48 trials between 2003 and 2015, with probable considerable overlap in patient population from the De Velasco et al study. Although most findings were similar, Khoja et al's findings deviated slightly when analyzing irAE incidence according to tumor histology in patients treated with PD-1 inhibitors. They found that patients with melanoma experienced higher incidence of GI and skin irAEs but a lower incidence of pneumonitis compared with patients with non–small cell lung cancer (NSCLC). Patients with melanoma experienced arthritis and myalgia more commonly than those with renal cell carcinoma (RCC), but patients with RCC experienced

Dermatologic Toxicity



[e] See Principles of Immunosuppression (IMMUNO-A, available online, in these guidelines, at NCCN.org).
[f] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[g] Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[h] Characterized by an intense itching sensation.
[i] Mild or localized.
[j] Intense or widespread; intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); limiting iADLs.
[k] Intense or widespread; constant; limiting self-care ADLs or sleep. Assess serum IgE and histamine; consider oral antihistamines for increased histamine and omalizumab for increased IgE.
[l] Consider holding in select cases.

ICI_DERM-2

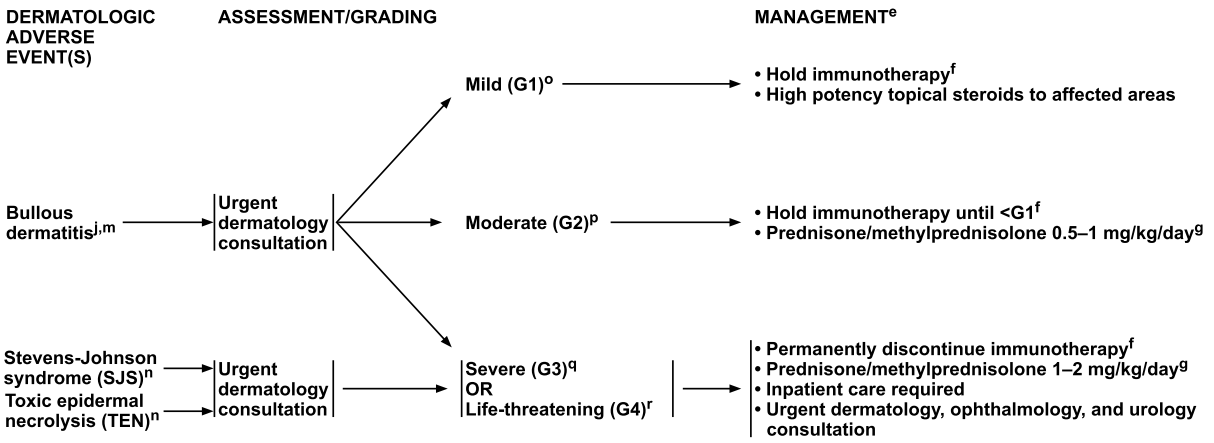
higher frequency of pneumonitis and dyspnea. However, comparisons of irAE incidence across disease type were not adjusted for patient factors such as smoking history and age. Similar comparisons were not possible for CTLA-4 blockade because most of the available data were on patients with melanoma.[40]

The safety data for PD-L1 inhibitors are still maturing, and data collection is ongoing. Comparison of irAE incidence for PD-1 versus PD-L1 inhibitors have been calculated primarily from data published on patients with NSCLC. A 2018 meta-analysis compared the data on toxicity profiles of PD-1 and PD-L1 inhibitors from 23 studies that occurred between 2013 and 2016 (PD-1: n=3,284; PD-L1: n=2,460).[41] A near-significant trend revealed irAEs to be more common with PD-1 versus PD-L1 blockade (16% vs 11%; *P*=.07). However, the incidence of severe irAEs was not significantly different between PD-L1 and PD-1 inhibitors (5% vs 3%; *P*=.4). Pneumonitis occurred twice as often with PD-1 inhibitors (4% vs 2%; *P*=.01) and hypothyroidism was also more common with PD-1 inhibitors (6.7% vs 4.2%; *P*=.07).[41] Similar findings were reported in a 2017 meta-analysis of data on pneumonitis incidence with PD-1 inhibitors (12 trials, n=3,232) and PD-L1 inhibitors (7 trials, n=1,806).[42] For PD-1 versus PD-L1 inhibitors, the incidence for any-grade pneumonitis was 3.6% versus 1.3% (*P*=.001) and 1.1% versus 0.4% for high-grade pneumonitis (*P*=.02).[42]

Combination Therapy

Numerous ongoing studies are examining regimens that include ICIs given in combination with another ICI, chemotherapy, or targeted agent. Although combination regimens offer the potential for enhanced efficacy, in general, observed toxicity with ICI-based combination regimens is greater than that for ICI monotherapy. Combined PD-1 plus CTLA-4 blockade triggers substantially more irAEs than anti-PD-1 agents alone, with high-grade events reported for 55% to 60% of individuals receiving combination therapy versus 10% to 20% of individuals receiving anti-PD-1 monotherapy.[43–45] Studies have begun to investigate the extent to which combination therapies pose clinical safety and tolerability challenges, and whether these challenges will limit their usefulness as anticancer therapy.[46–49]

Dermatologic Toxicity



[e] See Principles of Immunosuppression (IMMUNO-A, available online, in these guidelines, at NCCN.org).
[f] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[g] Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[j] Intense or widespread; intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); limiting iADLs.
[m] Characterized by inflammation of the skin and the presence of bullae, which are filled with fluid.
[n] Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) should be treated as grade 3–4 bullous dermatitis. SJS, overlapping SJS/TEN, and TEN are characterized by separation of the dermis involving <10%, 10%–30%, and >30% BSA, respectively. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.
[o] Asymptomatic; blisters covering <10% BSA.
[p] Blisters covering 10%–30% BSA; painful blisters; limiting iADLs.
[q] Blisters covering >30% BSA; limiting self-care ADLs.
[r] Blisters covering >30% BSA; associated with fluid or electrolyte abnormalities; intensive care unit (ICU) care or burn unit indicated.

ICI_DERM-3

The only current FDA-approved regimen using combined ICI therapy is nivolumab plus ipilimumab for treating advanced melanoma, RCC, or microsatellite-unstable tumors.[50,51] Nivolumab plus ipilimumab resulted in enhanced survival outcomes compared with ipilimumab monotherapy in advanced melanoma.[45,52] In the phase III CheckMate 067 trial of nivolumab plus ipilimumab versus ipilimumab or nivolumab monotherapy (n=945, randomized in a 1:1:1 ratio), treatment-related AEs occurred in 96% of patients receiving combination therapy and 86% of those treated with monotherapy. Although no unique toxicities were identified in patients receiving ICI combination therapy, the incidence of high-grade irAEs for combination therapy (59%) was more than twice the incidence for single-agent nivolumab (21%) and ipilimumab (28%). The percentages of patients discontinuing treatment due to any-grade treatment-related AEs were 39%, 12%, and 16% for patients receiving combination therapy, nivolumab, and ipilimumab, respectively. Preliminary findings suggest that early discontinuation due to irAEs (after a median of 3 doses) may not compromise survival benefit, as evidenced by a 3-year survival rate of 67%.[45]

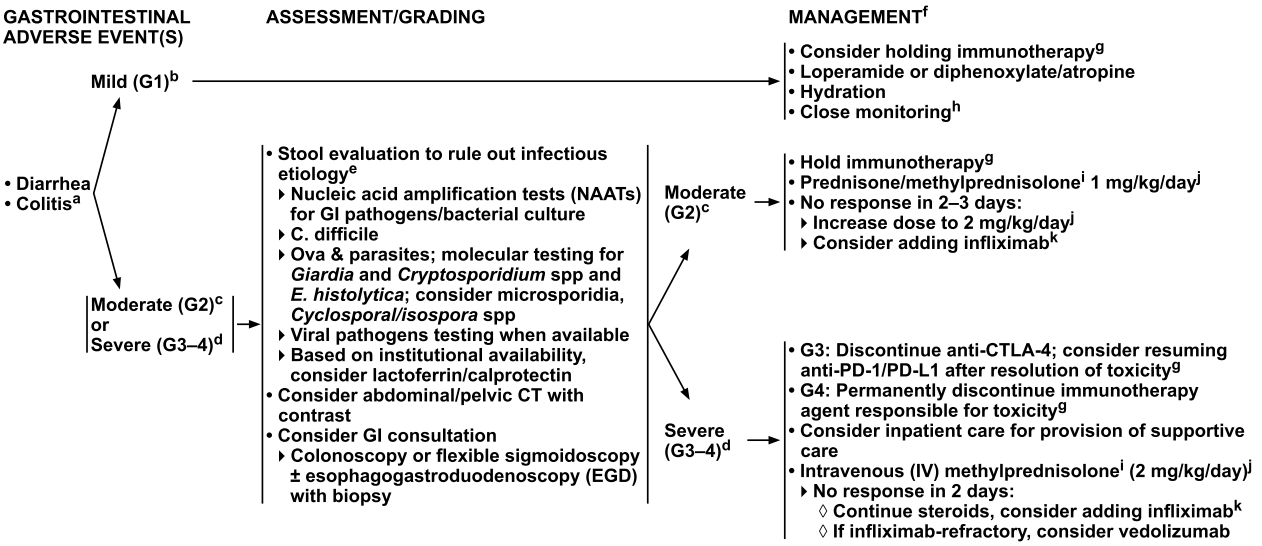
The KEYNOTE-029 trial began to investigate whether standard-dose pembrolizumab in combination with reduced-dose ipilimumab may be more tolerable than full-dose ICI combinations.[53] Dose-modified nivolumab plus ipilimumab regimens are also under investigation for NSCLC and small cell lung cancer,[54,55] and nivolumab plus ipilimumab is recommended in the NCCN Guidelines for Small Cell Lung Cancer.

Safety data have also been published for early-phase investigations of ICI therapy in combination with additional targeted agents or chemotherapeutics.[56–58] Immune checkpoint blockade given in combination with radiation therapy is also the subject of investigation.[59,60]

ICI Therapy-Related Fatal irAEs

A recently published systematic review and meta-analysis examined fatal irAEs from ICI therapy using data from multiple sources.[44] Meta-analysis of data from 112 published trials (n=19,217) compared the rate of fatal irAEs by agent. Similar rates of fatal irAEs were reported for anti-PD-1 (0.36%) and anti-PD-L1 agents (0.38%), with significantly higher rates of fatal irAEs

Gastrointestinal Toxicity



* Available online, in these guidelines, at NCCN.org.

[a] Symptoms include: watery diarrhea, cramping, urgency, abdominal pain, blood and mucus in the stool, fever. Blood in the stools and/or fever should prompt a more thorough workup for infection and for other causes of GI bleeding, including peptic ulcer disease (PUD) and malignant bleeding.

[b] Fewer than 4 bowel movements above baseline per day and no colitis symptoms.

[c] 4–6 bowel movements above baseline per day, colitis symptoms, not interfering with ADLs.

[d] More than 6 bowel movements above baseline per day, colitis symptoms, interfering with ADLs, hemodynamic instability, hospitalization, other serious complications (eg, ischemic bowel, perforation, toxic mega-colon).

[e] It is not necessary to wait for test results before providing therapy to manage immune-related adverse events (irAEs).

[f] See Principles of Immunosuppression (IMMUNO-A*).

[g] See Principles of Immunotherapy Rechallenge (IMMUNO-C).

[h] If progressive, consider stool evaluation to rule out infectious etiology.

[i] Convert to prednisone when appropriate.

[j] Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.

[k] Duration of therapy with tumor necrosis factor alpha (TNF-alpha) blockers is not clearly defined, but is usually a single dose. Repeat endoscopy may be helpful, but optional for the guidance of treatment. (See Principles of Immunosuppression [IMMUNO-A*] regarding TB testing.)

ICI_GI-1

reported for anti-CTLA-4 monotherapy (1.08%) and anti-PD-1/PD-L1 plus anti-CTLA-4 combination regimens (1.23%). For ipilimumab monotherapy, significantly fewer fatal irAEs occurred at the 3 mg/kg dose than 10 mg/kg dose. However, when used in combination with anti-PD-1 therapy, no significant difference in fatal irAE rate was observed for ipilimumab at 1mg/kg verus 3 mg/kg dose.[44]

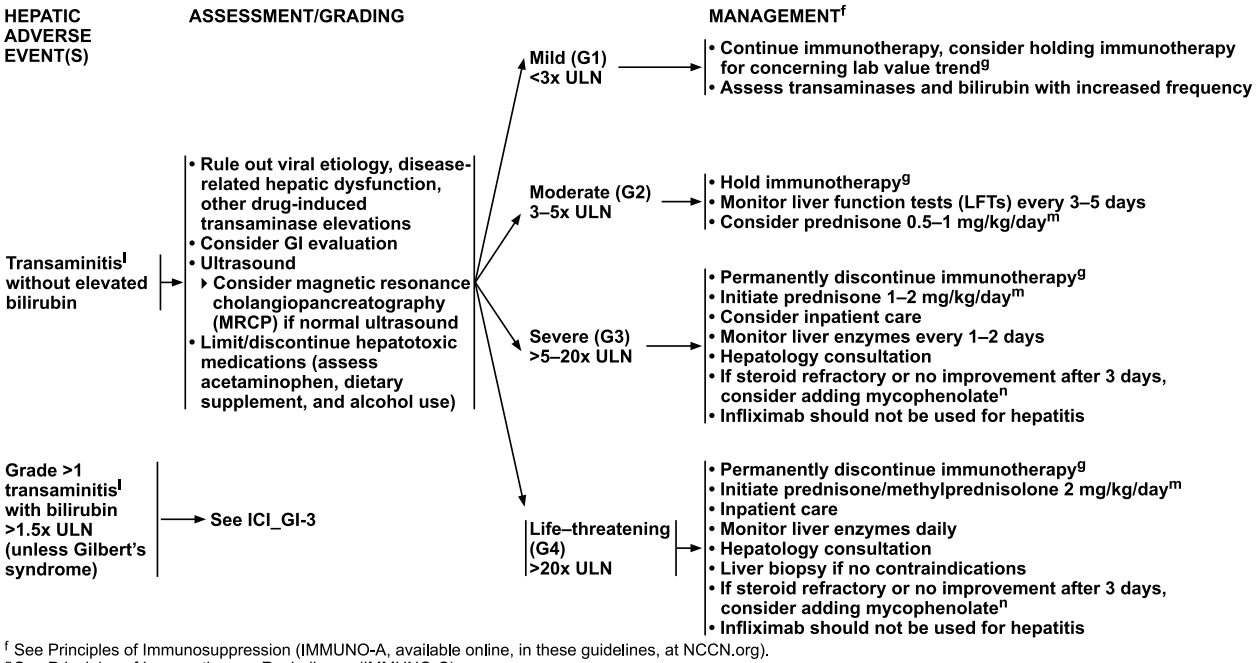
Examination of 613 cases of fatal ICI-related irAEs reported in the WHO pharmacovigilance database revealed that certain ICI agents were associated with a different spectrum of fatal irAEs.[44] The majority of fatal irAEs associated with ipilimumab monotherapy were due to colitis (70%), with smaller proportions of hepatitis and pneumonitis-related deaths. However, fatal irAEs with anti-PD-1/PD-L1 therapy were distributed more broadly: pneumonitis (35%), hepatitis (22%), colitis (17%), neurologic events (15%), and myocarditis (8%). Among the fatal irAEs reported for combination regimens (ipilimumab plus anti-PD-1/PD-L1), colitis was most common (37%), followed by myocarditis (25%), hepatitis (22%), pneumonitis (14%), and myositis (13%). When fatality rates were assessed across different types of irAEs, myocarditis was associated with the highest risk of death (52/131 cases, 39.7%). Fatality rates for patients with hepatitis, pneumonitis, nephritis, and neurologic events ranged between 10% and 17%, while ≤5% of hypophysitis, adrenal insufficiency, and colitis cases proved fatal.[44]

Finally, temporal patterns of fatal irAEs were examined using combined pharmacovigilance case reports and multicenter retrospective data review.[44] For irAEs that eventually proved fatal, symptom presentation occurred a median of 40 days after onset of monotherapy with ipilimumab or an anti-PD-1/PD-L1 agent, and 14.5 days after initiation of combination regimens. Median time to death after initiation of ipilimumab monotherapy, anti-PD-1/PD-L1 monotherapy, or combination regimen was 64, 43, and 35 days, respectively.[44]

IrAEs as a Biomarker of Treatment Response

Investigators have begun to examine whether developing certain ICI-mediated irAEs may be linked to improved treatment response and survival outcomes. An overview of the preliminary findings related to irAEs and treatment

Gastrointestinal Toxicity



[f] See Principles of Immunosuppression (IMMUNO-A, available online, in these guidelines, at NCCN.org).
[g] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[l] Elevated alanine transaminase (ALT) and aspartate transaminase (AST).
[m] When liver enzymes show sustained improvement or return to ≤ G1, initiate steroid tapering and continue to taper over at least 1 month with frequent follow-up to guide taper duration. Re-escalate as needed.
[n] Mycophenolate mofetil treatment (0.5–1 g every 12 hours) can be considered in patients who have persistent severe hepatitis despite high-dose corticosteroids.

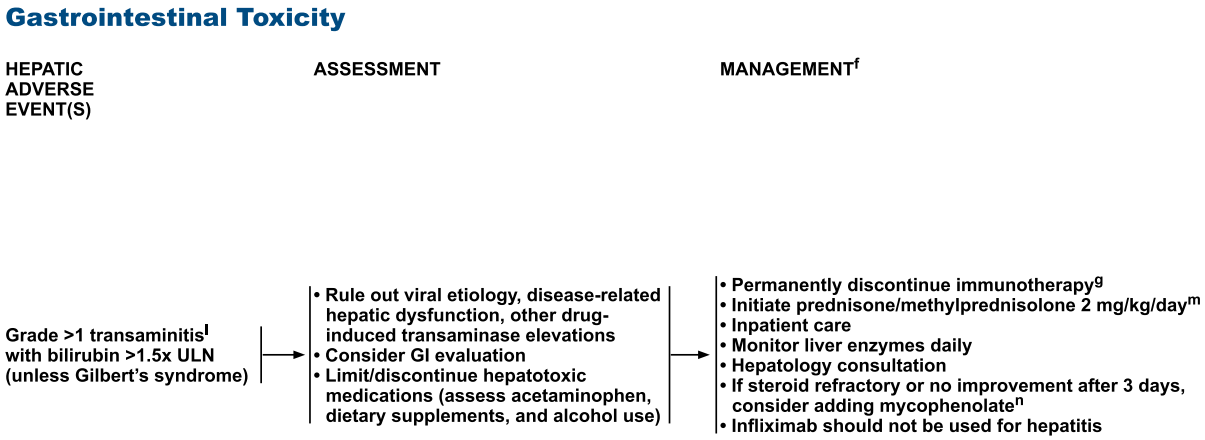
ICI_GI-2

outcomes is provided in the next paragraphs. Further research into this phenomenon is needed to explore potential patterns.

Historically, induction of cutaneous irAEs was suggested as a positive prognostic factor in patients with melanoma who received various types of immunotherapy.[61] A retrospective review found that cutaneous irAEs, particularly vitiligo, may be associated with improved treatment response with pembrolizumab.[62–64] In patients with melanoma who received nivolumab, rash and vitiligo were both associated with improved overall survival (OS).[65] The potential relationship between development of GI irAEs and survival outcomes has also been investigated. A retrospective analysis of 327 patients found an association between GI irAEs and OS, with diarrhea being an independent predictor of OS regardless of whether immunosuppressive therapy was required to manage this irAE.[66]

In a prospective cohort of 524 patients receiving ICI therapy, patients who developed rheumatologic irAEs had a higher tumor response rate compared with patients who experienced no irAEs (85.7% vs 35.3%; $P<.0001$).[67] Additionally, early data suggest a possible association between the development of neurologic irAEs and favorable disease response. Durable disease response has been reported in the setting of neurologic irAEs despite early discontinuation of ICI.[68]

However, in a retrospective review of 298 patients who received ipilimumab for metastatic melanoma, the occurrence of any-grade irAEs was not associated with OS or time to treatment failure (TTF).[69] The authors also found no association between systemic corticosteroid therapy to manage irAEs and OS or TTF. Along similar lines, investigators have also questioned the impact of early discontinuation of ICI due to toxicity on antitumor efficacy and safety. Schadendorf et al[30] examined pooled data from randomized phase II/III trials in which patients received combination nivolumab plus ipilimumab therapy (n=409). Therapy was discontinued due to AEs in 176 patients, including 96 patients who discontinued therapy during the induction phase (in which most high-grade AEs occurred). Overall response rate (ORR) was 58.3% for patients who discontinued therapy due to AEs during induction versus 50.2% for those who did not discontinue therapy. Although similar, median OS was not reached for either group.[30]



[f] See Principles of Immunosuppression (IMMUNO-A, available online, in these guidelines, at NCCN.org).
[g] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[l] Elevated ALT and AST.
[m] When liver enzymes show sustained improvement or return to ≤ G1, initiate steroid tapering and continue to taper over at least 1 month. Re-escalate as needed.
[n] Mycophenolate mofetil treatment (0.5–1 g every 12 hours) can be considered in patients who have persistent severe hepatitis despite high-dose corticosteroids.

ICI_GI-3

Management of ICI-Related Toxicity

The primary facets of irAE management include recognition and grading of toxicity, immunosuppression, and individualized modification to ICI administration. Early recognition of symptoms and prompt intervention are key goals for the management of immunotherapy-related toxicity. Significant irAEs often necessitate holding immunotherapy, with permanent discontinuation of the class of agent associated with the toxicity in the setting of certain severe irAEs.

General Principles of Immunosuppression

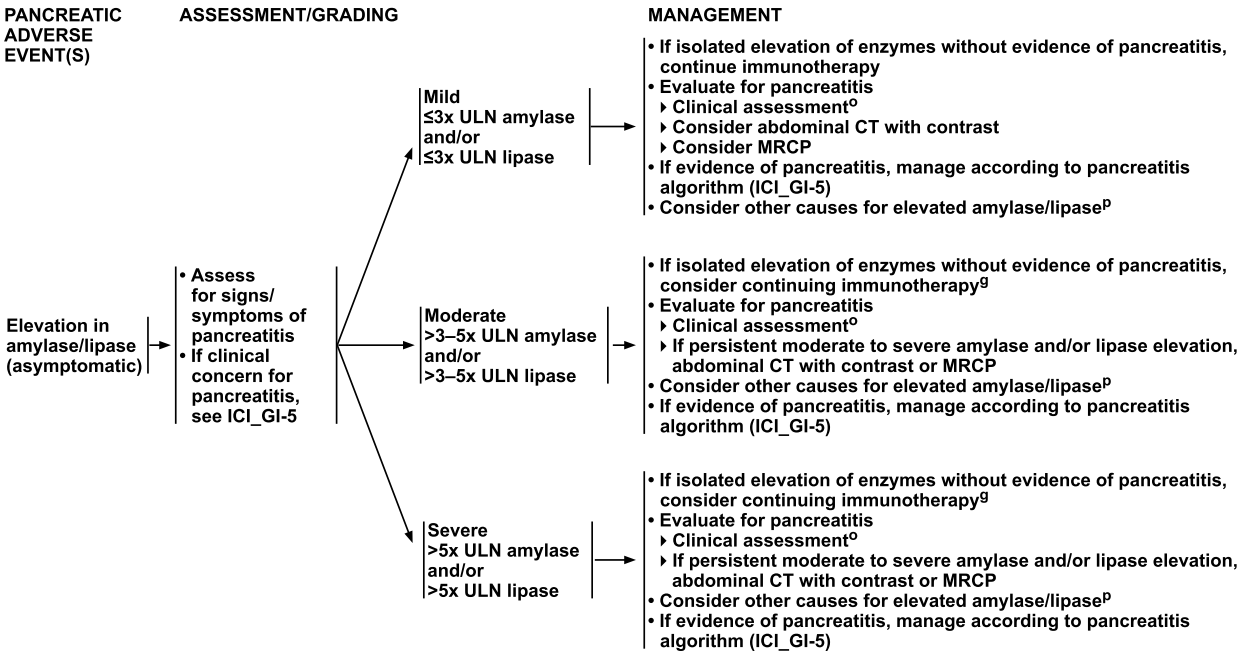
Corticosteroids are the mainstay of treatment of most high-grade irAEs. Importantly, short-term use of corticosteroids to treat irAEs has not been shown to reduce antitumor efficacy. Appropriate duration and careful taper of corticosteroid therapy is important to prevent the recurrence of irAEs. For most irAEs, slow corticosteroid taper is recommended to adequately resolve toxicity and prevent recurrence. Unless otherwise indicated in the algorithm, patients should be tapered off corticosteroid with resolution of symptoms before considering immunotherapy resumption. Severe or steroid-refractory irAEs may require administration of additional immunosuppressive agents. For patients with severe irAEs not responsive to steroids within 48 to 72 hours, initiation of an additional immunosuppressant agent may be warranted, in consultation with the relevant medical specialist. Close monitoring and follow-up should be performed to assess for response to corticosteroids and other immunosuppressants in the setting of ICI-related toxicity.

Tailored recommendations regarding the use of nonsteroid immunosuppressants can be found in the individual irAE treatment algorithms and corresponding discussion sections. Selected endocrine irAEs may be treated with hormonal supplementation without the need for immunosuppression.

Immunomodulators

In these guidelines, recommendation for use of specific immune-modulating agents to manage irAEs are typically extrapolated from evidence for treating autoimmune conditions of the relevant organ system(s). Several commonly used immunosuppressants for

Gastrointestinal Toxicity



[g] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[o] Routine amylase/lipase assessments do not have to be performed outside of clinical suspicion of possible pancreatitis. See Principles of Routine Monitoring (IMMUNO-1).
[p] Inflammatory bowel disease, irritable bowel syndrome, bowel obstruction, gastroparesis, nausea/vomiting, medications, alcohol, and/or diabetes mellitus (DM).

ICI_GI-4

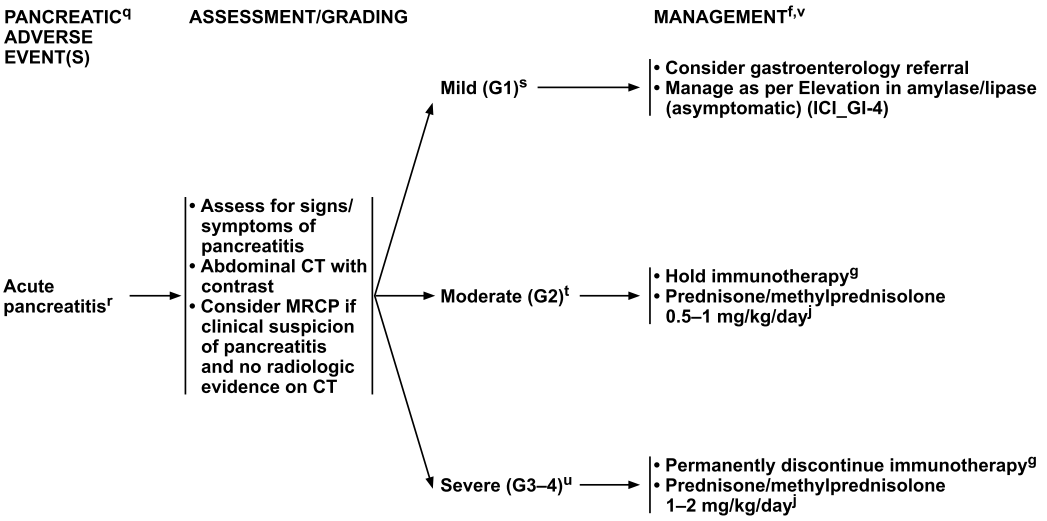
managing steroid-refractory or severe irAEs are discussed in this section.

Tumor necrosis factor (TNF) inhibitors are a class of drugs widely used to block the inflammatory effects of TNF in autoimmune diseases.[70] Infliximab is a monoclonal anti-TNF-α antibody used for treating various autoimmune diseases, including Crohn's disease, ulcerative colitis, rheumatoid and psoriatic arthritis, and psoriasis.[70–72] Infliximab blocks the interaction of TNF-α with its receptors, inhibiting induction of proinflammatory cytokines (IL-1, IL-6) and modulating the activity of immune effectors such as leukocytes, neutrophils, and eosinophils.[72,73] Infliximab has become a commonly used agent for treating steroid-refractory irAEs that develop during ICI therapy.[17,74] For patients with severe irAEs not responsive to steroids within 48 to 72 hours, early initiation of anti-TNF-α therapy (ie, at 72 hours) may be warranted in consultation with the relevant medical specialist. Duration of therapy with TNF-α blockers for irAEs is not clearly defined but is typically a single dose. A second dose of anti-TNF-α therapy may be required and can be administered 2 weeks after the initial dose of infliximab. Anti-TNF-α agents (eg, infliximab) are particularly effective in management of immune-related colitis and inflammatory arthritis (IA). At present, infliximab is not recommended for managing immune-related hepatitis.

Vedolizumab is an integrin antagonist that binds to α4β7 integrin, blocking its interaction with mucosal addressin cell adhesion molecule-1, inhibiting the migration of T cells across the endothelium into inflamed GI tissues. Vedolizumab is currently indicated for treating GI inflammation due to ulcerative colitis and Crohn's disease.[75,76] Case reports have described the use of vedolizumab for treating ICI-induced enterocolitis.[76,77] Vedolizumab may provide more specific immune suppression for the inflamed GI mucosa, hence theoretically sparing systemic immune suppression and antitumor immune responses.

Mycophenolate-containing medicines are immunosuppressive agents used for preventing organ rejection after transplant (ie, kidney, heart, liver). It is available as mycophenolic acid or as mycophenolate mofetil, a prodrug of mycophenolic acid.[78,79] These agents have

Gastrointestinal Toxicity



[f] See Principles of Immunosuppression (IMMUNO-A, available online, in these guidelines, at NCCN.org).
[g] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[j] Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[q] No requirement for routine monitoring of potential pancreatitis with imaging.
[r] Provide standard medical care for signs and symptoms of acute pancreatitis, including hospital admission, aggressive fluid resuscitation, and pain control. Management and follow-up of pancreatitis should be directed by gastroenterology/pancreatic subspecialists.
[s] Any one of the following features present: elevation of amylase/lipase >3x ULN or radiologic findings on CT or clinical findings concerning for pancreatitis.
[t] Two of three of the following features present: elevation of amylase/lipase >3x ULN ± radiologic findings on CT ± clinical findings concerning for pancreatitis.
[u] Elevation of amylase/lipase ± radiologic findings ± severe abdominal pain or vomiting and hemodynamically unstable.
[v] Evaluate for signs/symptoms of pancreatic exocrine insufficiency and/or DM, and supplement if needed.

ICI_GI-5

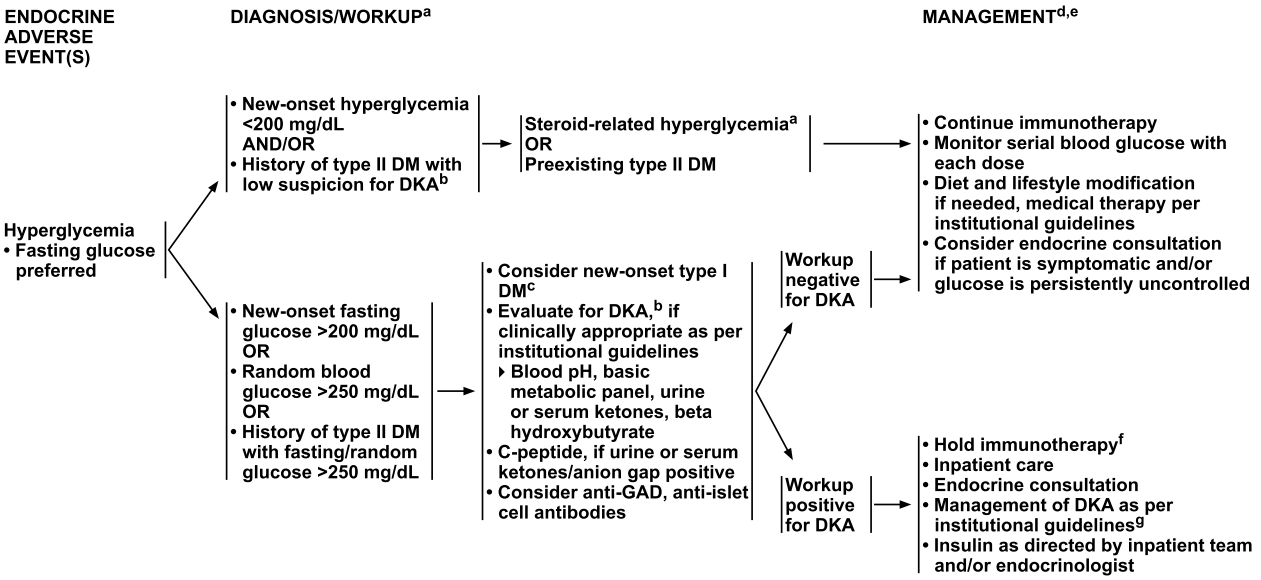
multiple immunosuppressive actions, which result in decreased B- and T-cell proliferation, T-cell apoptosis, and suppression of dendritic cells and IL-1.[80,81] Published studies also support the clinical efficacy of these mycophenolate drugs in various inflammatory or autoimmune conditions, such as autoimmune hepatitis, myositis, bullous disease, interstitial lung disease, and lupus nephritis, among others.[82–87] Retrospective analyses and case reports describe the use of mycophenolate in the management of steroid-refractory irAEs, including those involving the liver, kidney, pancreas, and eyes.[43,88–91]

Intravenous immunoglobulin (IVIG) has been used to suppress a wide array of autoimmune and chronic inflammatory conditions.[92,93] It is comprised of pooled immunoglobulin G harvested from the plasma of healthy blood donors and prepared for intravenous administration. The immunomodulatory mechanisms of IVIG are not fully understood, but it is known to modulate the activity and effector functions of B- and T-lymphocytes, impacting antigen presentation, pathogenic autoantibodies, complement system, and cytokines.[93–95] Efficacy has been demonstrated in neurologic inflammatory or autoimmune conditions such as Guillain-Barré syndrome (GBS), myasthenia gravis, neuropathies, rheumatologic conditions, blistering disorders, immune hematologic conditions, and many others.[96,97]

Plasmapheresis is a type of therapy that may be indicated when a substance in the plasma, such as immunoglobulin, becomes acutely toxic, as can occur during certain autoimmune reactions. During plasmapheresis, the blood contents are separated extracorporeally, resulting in removal of the plasma and subsequent therapeutic plasma exchange via infusion. Indications for which this procedure is a first-line therapy include neurologic conditions such as myasthenia gravis and GBS, but it is also indicated for various other autoimmune conditions.[98] Plasmapheresis (and IVIG) is often indicated as a second-line therapy for managing neurologic irAEs after limited or nonresponse to initial high-dose corticosteroid.[99] However, success in treating severe and often rapidly progressive neurologic irAEs has been mixed.[99–101]

Additional agents that have been used less frequently as part of advanced lines of immunosuppressive

Endocrine Toxicity



[a] High-dose corticosteroids may induce or exacerbate hyperglycemia. Consider endocrinology referral and appropriate management if symptomatic and/or persistently uncontrolled.
[b] Symptoms of diabetic ketoacidosis (DKA) may include excessive thirst, frequent urination, general weakness, vomiting, confusion, abdominal pain, dry skin, dry mouth, increased heart rate, and fruity odor on the breath.
[c] The development of type I DM is rare (1%–2%) but can be life-threatening if insulin therapy is not provided. Once new type I DM is diagnosed, management and monitoring should be directed by endocrinology team.
[d] Evaluate for signs/symptoms of pancreatic exocrine insufficiency, and supplement if needed.
[e] Insufficient evidence to suggest corticosteroids may reverse type I DM induced by immunotherapy, and may complicate glycemic control.
[f] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[g] Institutional guidelines may include but are not limited to: IV fluids +/– potassium supplementation, IV insulin, hourly glucose, serum ketones, blood pH, and anion gap.

ICI_ENDO-1

therapy include rituximab, tacrolimus, tocilizumab, cyclosporine, cyclophosphamide, methotrexate, and antirheumatic agents (eg, sulfasalazine, leflunomide).

Considerations for Patients on Immunosuppressants

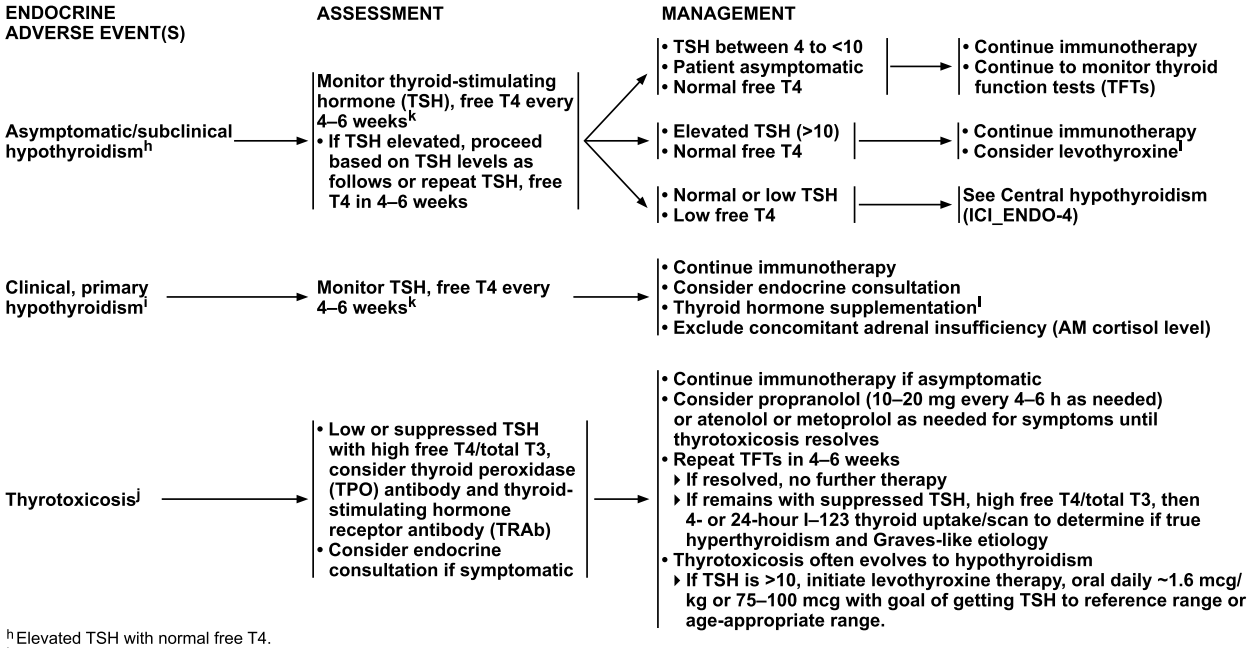
Additional supportive care measures are needed for patients receiving an immunosuppressive regimen. Hyperglycemia, gastritis, opportunistic bacterial or fungal infections, and osteoporosis can occur with a longer-term systemic corticosteroid.[102–107] The panel recommends blood glucose monitoring and various prophylactic measures. For patients at higher risk of developing gastritis (ie, those taking nonsteroidal anti-inflammatory drugs or anticoagulants), histamine 2 blockers or proton pump inhibitors can be given during steroid therapy. Consider prophylactic antimicrobial and antifungal agents. Prophylaxis against pneumocystis jiroveci pneumonia should be considered in patients receiving a prednisone equivalent of ≥20 mg/day for 4 or more weeks, with general prophylaxis against fungal infections (ie, fluconazole) for patients receiving a prednisone equivalent of ≥20 mg/day for 6 or more weeks. Consider prophylaxis against zoster reactivation. Finally, vitamin D and calcium supplementation is recommended to reduce the risk of osteoporosis.

Anti-TNF-α therapy may pose a risk of reactivating viral infections such as viral hepatitis or tuberculosis.[108–111] The panel recommends testing for hepatitis B and C virus before TNF inhibition, and carriers should be monitored during and for several months after immunosuppressive therapy. Additionally, testing for latent/active tuberculosis is recommended before start of infliximab therapy; IFN-gamma release assays are preferred. However, tuberculosis testing should not delay initiation of anti-TNF-α agents for the management of acute severe or refractory irAEs.

Impact of Immunosuppressive Agents on Immunotherapy Efficacy

Although no prospective data exist, retrospective data generally suggest that immunosuppressive therapy started after onset of irAEs does not appear to decrease ICI efficacy. Results were recently published from a pooled analysis of 4 studies enrolling 576 patients who received

Endocrine Toxicity



[h] Elevated TSH with normal free T4.
[i] Generally, elevated TSH (>10) with low free T4, clinical symptoms.
[j] Defined as suppressed TSH that may be: a) subclinical if free T4 normal, b) clinical if high free T4. The majority of suppressed TSH (<0.01) are due to transient or progressive painless thyroiditis.
[k] For patients without baseline thyroid function abnormalities or who are asymptomatic, can increase thyroid function testing interval to every 12–18 weeks as indicated.
[l] Levothyroxine oral daily ~1.6 mcg/kg with goal of getting TSH to reference range or age-appropriate range; reduce dose by 10% to avoid hyperthyroidism in patient populations that may be sensitive to thyroid supplementation (eg, elderly populations or patients with comorbidities).

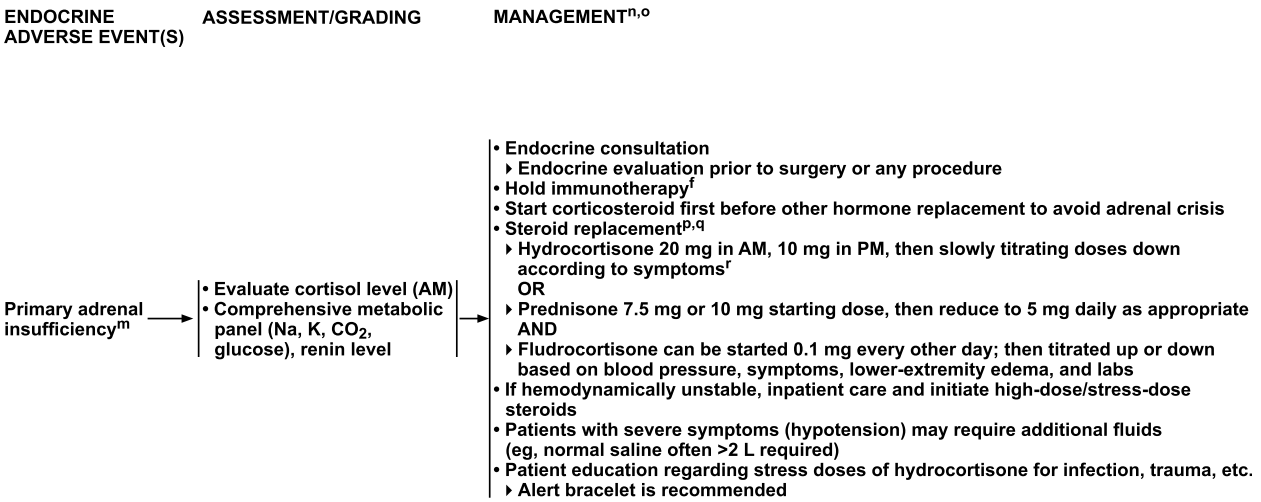
ICI_ENDO-2

nivolumab for advanced melanoma.[112] When adjusting for the number of nivolumab doses, ORR was higher among patients who experienced all-grade irAEs compared with those who did not. Among the 474 phase III trial participants, 114 (24%) received systemic corticosteroids for managing irAEs. ORR was not significantly different between patients who required corticosteroids and those who did not.[112] Similar findings were reported by an earlier retrospective analysis of 298 patients with metastatic melanoma who were treated with ipilimumab.[69] Within this cohort, 103 (35%) required corticosteroid therapy to manage irAEs, and 29 of these patients (10%) also required anti-TNF-α therapy to address unresolved symptoms. OS and TTF were not impacted by the development of irAEs or the need for corticosteroid therapy to manage them.[69] Similarly, among a pooled group of 409 patients who received nivolumab plus ipilimumab combination therapy as part of CheckMate 067 and 069, ORR was not reduced among patients who required corticosteroid therapy to manage irAEs relative to the rest of the cohort.[30,113]

Investigators have also analyzed whether immunosuppression via TNF antagonist had a negative impact on combination ICI therapy response. Based on retrospective analysis of data from CheckMate 067 and 069, using infliximab to manage colitis did not appear to alter the kinetics of tumor response or durability.[30] Another analysis of pooled data from these trials showed similar survival outcomes between patients with GI irAEs who received corticosteroid therapy with or without infliximab and patients with GI irAEs who did not receive immunosuppressive agents.[113]

Due to clinical trial exclusion criteria, less is known about the impact of immunosuppressants on ICI efficacy when given before ICI therapy. A recent retrospective study identified 90 individuals who were on baseline corticosteroid therapy (≥10 prednisone equivalent daily) from a cohort of 640 patients with NSCLC on anti-PD-1/PD-L1 monotherapy. Baseline corticosteroid therapy was associated with poorer outcomes from ICI therapy, as indicated by decreased ORR, progression-free survival, and OS.[114] Additional research will be needed to better understand the potential impact of corticosteroid exposure before or during ICI therapy initiation, especially as it pertains to premedication with corticosteroid before ICI infusion.

Endocrine Toxicity



[f] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[m] Low morning cortisol (<5) with high ACTH (> reference range) with or without abnormal electrolytes and symptoms. Other criteria: 30- or 60-minute cortisol <18 after ACTH stimulation in the setting of low morning cortisol and high ACTH. Other abnormalities: hypotension, orthostatic hypotension, low Na, and high K.
[n] See Principles of Immunosuppression (IMMUNO-A, available online, in these guidelines, at NCCN.org).
[o] If severe acute symptoms (eg, headache/nausea/emesis, fevers), high-dose steroids as indicated until symptoms resolve (1–2 weeks) then rapid taper to physiologic replacement.
[p] If acutely ill, double or triple these doses for 24–48 hours (ie, sick day rules for fever >101, nausea/emesis, surgeries).
[q] Will require physiologic replacement steroids indefinitely.
[r] The goal for physiologic steroid replacement is to identify the lowest steroid dose needed to prevent symptoms of adrenal insufficiency. For many patients, this may be, for example, 10 mg in AM and 5 mg in PM, if tolerated.

ICI_ENDO-3

Managing irAEs in Special Patient Populations

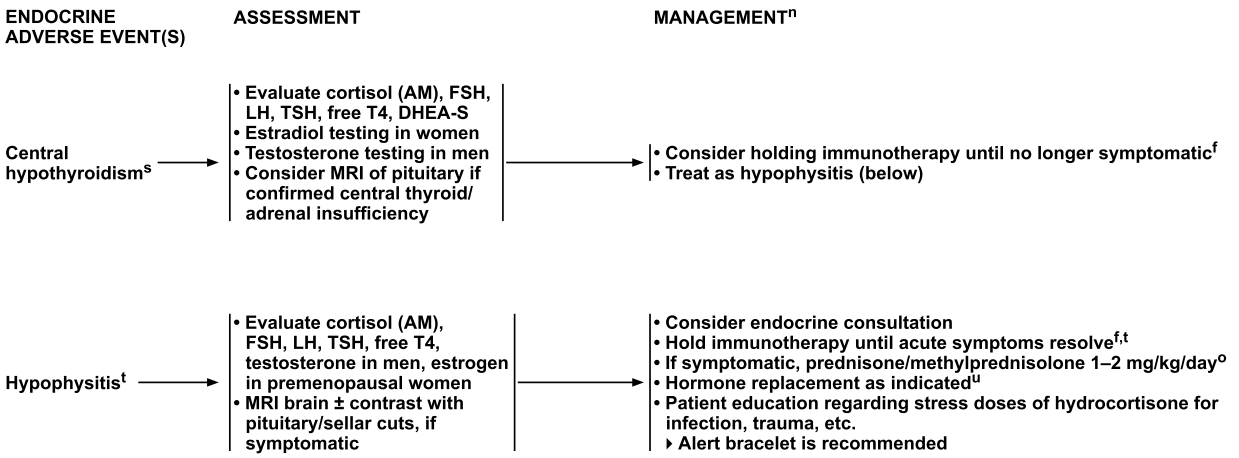
Patients With Prior irAEs or Pre-existing Autoimmune Conditions

In patients with pre-existing autoimmune disease, exacerbation of autoimmunity is a concern with the administration of immune-activating agents. Similarly, ICI therapy must be approached cautiously among patients who have experienced a prior irAE while receiving immunotherapy. Data on the toxicity of ICIs in patients with pre-existing autoimmune disease or irAEs is generally lacking due to exclusion of these populations from clinical trials leading to FDA approval. Based on limited data from smaller retrospective studies, ICIs appear to be similarly effective in these patient groups with response rates of 20% to 40%.[115–117] Based on the available data, most autoimmune disease flares and irAEs in this patient population have been managed with corticosteroid or additional immunosuppressive therapy; however, fatal AEs have been reported.[118] Preliminary data on safety and toxicity are described subsequently.

In the largest series to date, ipilimumab therapy was provided to a cohort of 30 patients with advanced melanoma and pre-existing autoimmune disorders, including inflammatory bowel disease (n=6), rheumatoid arthritis (n=6), psoriasis (n=5), systemic lupus erythematosus (n=2), multiple sclerosis (n=2), autoimmune thyroiditis (n=2), and various others.[117] Thirteen of 30 patients were taking immunosuppressive therapy to manage their conditions. While on ipilimumab, 27% of patients experienced exacerbation of their autoimmune condition, typically in the form of recurrent or enhanced pre-existing symptoms. Most were managed successfully using corticosteroid, with 2 patients requiring infliximab. Ten patients (33%) experienced conventional high-grade irAEs considered unrelated to their baseline autoimmune condition (including one fatality due to colitis in a patient with skin-limited psoriasis). Three patients experienced concurrent autoimmune condition flares and conventional irAEs requiring high-dose corticosteroid. However, half of the cohort experienced no irAEs or autoimmune condition flare.[117]

Studies have also examined the effects of PD-1 inhibitors for advanced melanoma in patients with pre-existing autoimmune disease.[115,116] Among a subset of

Endocrine Toxicity



[f] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[n] See Principles of Immunosuppression (IMMUNO-A, available online, in these guidelines, at NCCN.org).
[o] If severe acute symptoms (eg, headache/nausea/emesis, fevers), high-dose steroids as indicated until symptoms resolve (1–2 weeks) then rapid taper to physiologic replacement.
[s] Low or suppressed TSH with inappropriately low free T4 may represent sequela of hypophysitis; for which other pituitary axes may be affected. Follow free T4 for thyroid replacement in the setting of hypophysitis–induced loss of TSH production.
[t] Hypophysitis may present with acute symptoms such as headache, photophobia, dizziness, nausea/emesis, fevers, anorexia, visual field cuts, or severe fatigue. Tests may show low ACTH, low AM cortisol, low Na, low K, low testosterone, and DHEA-S. Non-acute symptoms may include fatigue and possible weight loss.
[u] Hormone replacement for pituitary damage should include steroid replacement (hydrocortisone 20 mg PO every AM, 10 mg PO every PM); it may also include levothyroxine for central hypothyroidism and testosterone supplementation in males. Patients may require physiologic replacement hormones indefinitely.

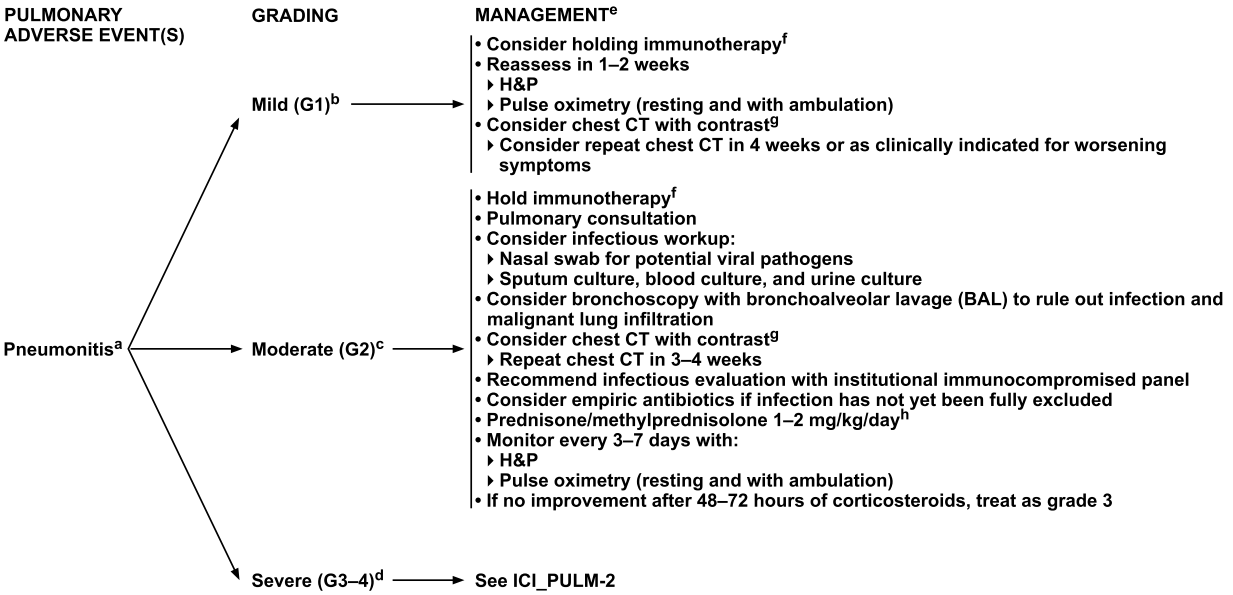
ICI_ENDO-4

19 patients with prior autoimmune disease, PD-1 inhibition led to autoimmune flare in 42%, and onset of a new irAE in 16%.[115] In a separate study of 52 patients with significant autoimmune conditions (eg, rheumatoid arthritis, polymyalgia rheumatica, Sjögren's syndrome, immune thrombocytopenic purpura, psoriasis), 38% had an autoimmune condition flare requiring immunosuppression, and 29% developed a new irAE.[116] Interestingly, no members of that cohort with GI or neurologic autoimmune conditions (n=11) experienced a flare.[116] In both studies of PD-1 inhibitors, most flares of pre-existing autoimmune conditions were adequately managed using immunosuppressive and symptomatic therapy.[115,116] However, onset of new irAEs led to discontinuation of PD-1 inhibitor in about 10% of patients in 1 study.[116]

Reviews of the data have also probed the impact of PD-1 inhibitor therapy for treating melanoma in patients who developed prior treatment-related irAEs during ipilimumab monotherapy or combination CTLA-4/PD-1 blockade.[115,116,119] Among the 22 patients with ipilimumab-related irAEs described by Gutzmer et al,[115] treatment with a PD-1 inhibitor led to a flare of the prior irAE in 4.5% of patients, whereas 23% developed a new irAE. In another study of 67 patients with prior ipilimumab-related irAEs requiring immunosuppression, flare was reported in 3% of patients, and 34% developed new irAEs.[116]

Nivolumab or pembrolizumab monotherapy was resumed in a cohort of 80 patients who had previously discontinued combination ICI therapy due to irAEs.[119] On resumption of PD-1 inhibition, 14 patients (18%) experienced a recurrence of the same irAE and 17 patients (21%) experienced clinically significant "distinct" or de novo irAEs. Half of the cohort (n=40) experienced any-grade irAE, with high-grade toxicity in 18% (n=14). Twenty-four patients (30%) discontinued PD-1 monotherapy due to irAE. Colitis and neurologic toxicities were found to be least likely to recur, whereas hepatitis, pancreatitis, nephritis, and pneumonitis recurred more commonly. Symptomatic hypophysitis and rash were assessed as intermediate risk for recurrence; however, 1 fatality occurred due to recurrent and worsening rash and bullous disease. Due to the relatively high rate of severe but distinct irAEs that were observed during anti-PD-1 agent

Pulmonary Toxicity



[a] Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging as ground-glass opacities).
[b] Asymptomatic; confined to one lobe of the lung or <25% of lung parenchyma; clinical or diagnostic observations only.
[c] Presence of new/worsening symptoms including: shortness of breath, cough, chest pain, fever, and increased oxygen requirement.
[d] G3-severe symptoms involve all lung lobes or >50% of lung parenchyma, limiting self-care ADLs; G4–life-threatening respiratory compromise.
[e] See Principles of Immunosuppression (IMMUNO-A, available online, in these guidelines, at NCCN.org).
[f] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[g] CT with contrast to rule out other etiologies if not contraindicated.
[h] Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.

ICI_PULM-1

rechallenge (21%), the authors posited 2 potential explanations. First, patients could be predisposed to subsequent toxicity due to immune priming by ICI combination therapy, and second, delayed presentation of irAEs due to combination therapy-related toxicity could have occurred.[119] Additional research is needed to understand the safety of ICI therapy in this population and others at a potentially greater risk for developing irAEs.

Organ Transplant Recipients

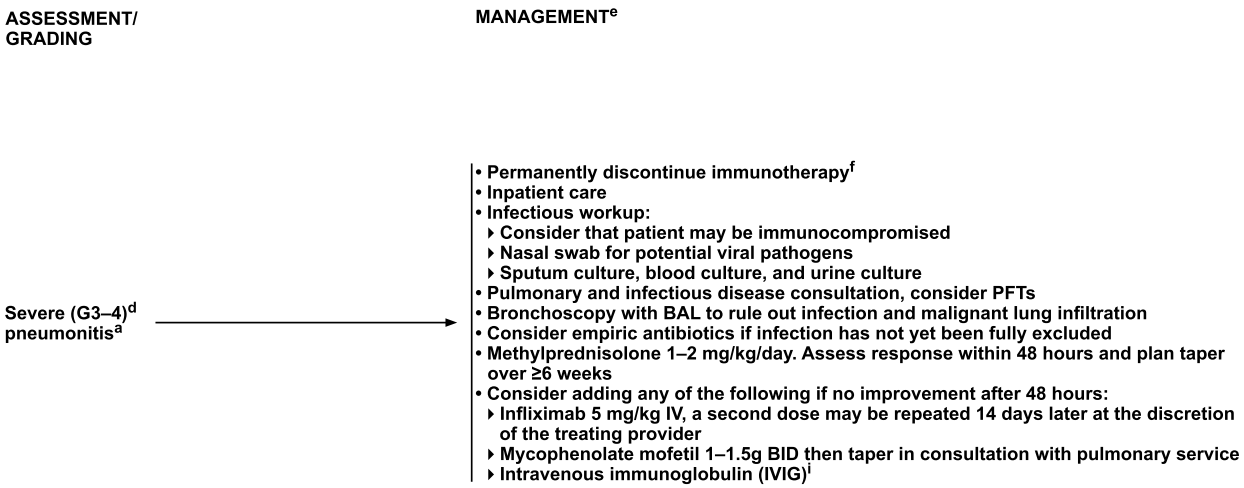
Concerns regarding graft rejection in transplant recipients has led to the exclusion of this patient population from many clinical trials of ICI therapy.[120] Safety and efficacy data on ICI therapy in patients who have received a prior organ transplant are limited to a small number of case reports. Safe ipilimumab use has been reported in several patients who received kidney or liver transplants.[120–123] A 2017 review of 12 case reports on ICI use in transplant recipients identified 4 patients who experienced kidney graft rejection after combination CTLA-4/PD-1 blockade or anti-PD-1 monotherapy.[120] PD-1 inhibition appears to be more commonly associated with graft rejection, suggesting that this pathway may play a more critical role in allograft immune tolerance.[120,124] Other factors to consider in organ transplant recipients who may be candidates for ICI therapy may include elapsed time between transplant and initiation of immunotherapy, the strength of maintenance immunosuppressive therapy required to prevent graft rejection, and the immunogenicity of the transplanted organ.[120,121]

Research is underway to explore alternative immunosuppressive regimens in an effort to reduce allograft rejection during ICI therapy.[121,124] The safety and utility of immunotherapy is also being investigated in patients with multiple myeloma who may be unable to mount an adequate immune response. In KEYNOTE 183 and KEYNOTE 185, more deaths were seen for treatment arms in which pembrolizumab was added to lenalidomide/dexamethasone or pomalidomide/dexamethasone.[125]

Specific irAE Management

In general, close consultation with disease-specific subspecialists is encouraged during irAE management. Referral to a tertiary care center may be required for

Pulmonary Toxicity



[a] Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging as ground-glass opacities).
[d] G3-severe symptoms involve all lung lobes or >50% of lung parenchyma; limiting self-care ADL; G4–life-threatening respiratory compromise.
[e] See Principles of Immunosuppression (IMMUNO-A, available online, in these guidelines, at NCCN.org).
[f] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[i] Total dosing should be 2 g/kg, administered in divided doses per package insert.

ICI_PULM-2

management of complex cases or multisystem irAEs. Due to the kinetics of the immune response, the onset of irAEs can occur at any point during treatment or even after completion of therapy.[126,127] irAE rebound during steroid taper has also been reported. The typical timing and presentation of specific irAEs are discussed in the next section. Please see the corresponding algorithm pages in the guidelines for detailed recommendations on assessing and treating particular irAEs by grade/severity.

Caution and careful judgment are required when considering whether to resume immunotherapy after significant toxicity. Clinicians should assess patient's tumor status before rechallenge. If an objective response (complete or partial) to ICI therapy was achieved, resumption of immunotherapy may not be advisable due to risk of toxicity recurrence. The NCCN Panel recommends that clinicians discuss the risks/benefits of restarting immunotherapy with the patient.

Infusion-Related Reactions

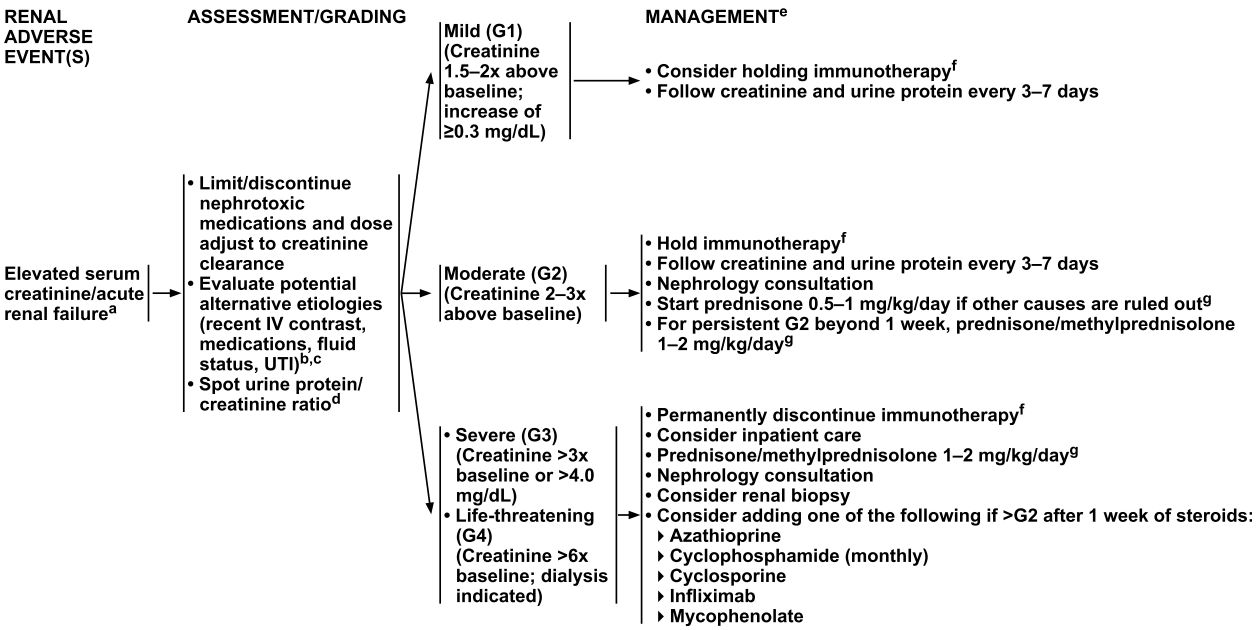
Infusion reactions have been reported most commonly with the PD-L1 inhibitor avelumab. Pooled safety data on avelumab reported that 25% of patients experienced any-grade infusion reactions (439/1,738) with high-grade events in 0.7% (12/1,738); most occurred during the first infusion, with nearly all reactions occurring within the first 4 treatment cycles.[128,129] Premedication appeared to decrease the rate of severe infusion-related reactions.[128] The U.S. prescribing instructions for avelumab include acetaminophen and diphenhydramine before infusion during the first 4 treatment cycles.[129]

Most infusion reactions associated with ICIs are mild and associated with low-grade fever, chills, headache, or nausea. Severe or high-grade reactions occurred in <1% of patients across all other ICIs. Incidence of any-grade infusion reactions for the remaining ICIs include atezolizumab at 1.3%, durvalumab at 2.2%, <10% for PD-1 inhibitors, and <1% for ipilimumab monotherapy.[1,50,51,130–132]

Dermatologic Toxicity

Dermatologic toxicities are the most prevalent irAEs associated with ICI therapy. Inflammatory skin conditions typically present within the first 2 cycles of

Renal Toxicity



[a] Azotemia, creatinine elevation, inability to maintain acid/base or electrolyte balance, and urine output change.
[b] General medical review and testing as warranted for prerenal and postrenal causes. Include medication review for nephrotoxic agents such as NSAIDS, and consider obstruction, cardiomyopathy/heart failure, pulmonary hypertension, diuretics, hypovolemia due to primary GI cause, stones, and infection.
[c] Distinguish cell infiltrate vs. immune-complex–mediated renal injury.
[d] For proteinuria >3 g/24-hour, check ANA, RF, ANCA, anti-dsDNA, and serum C3, C4, and CH50.
[e] See Principles of Immunosuppression (IMMUNO-A, available online, in these guidelines, at NCCN.org).
[f] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[g] Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.

ICI_RENAL-1

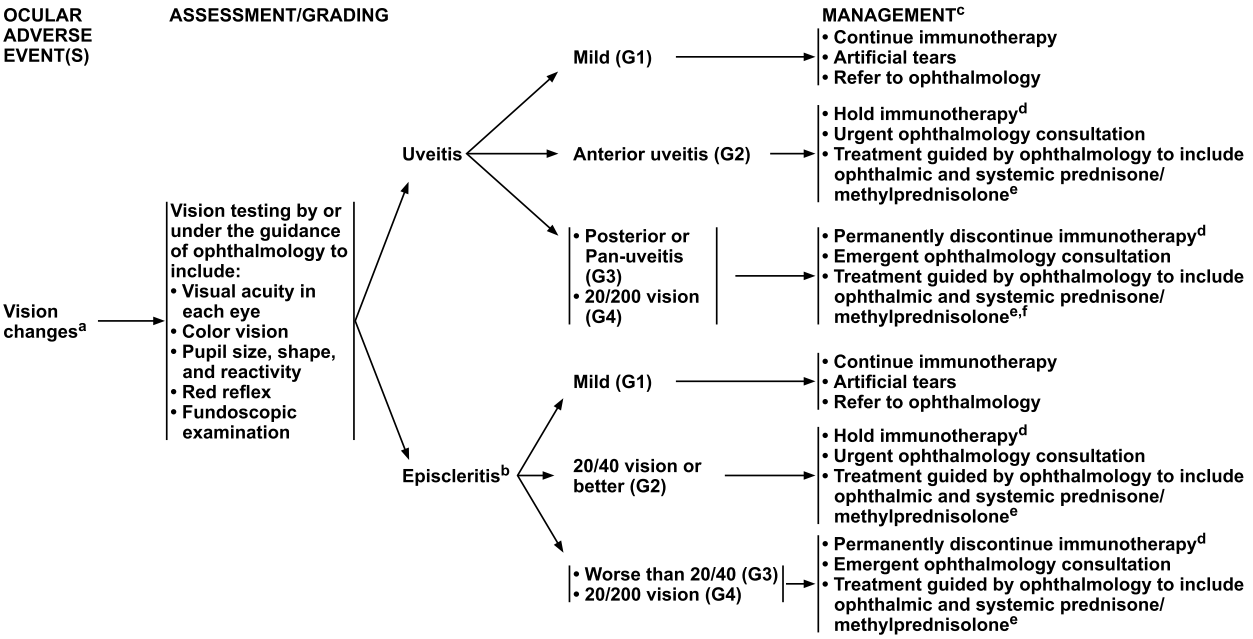
treatment (ie, within several weeks).[4,36,39,133,134] Ipilimumab has been consistently associated with higher rates of all-grade dermatologic irAEs than PD-1/PD-L1 inhibitors; reported incidences of all grade dermatologic toxicity range from 37% to 70% for ipilimumab and 17% to 40% for PD-1/PD-L1 inhibitors. The rates of high-grade dermatologic irAEs are similar across ICI classes and range from 1% to 3% for ipilimumab and PD-1/PD-L1 inhibitors.[2,29,36,135] Generally, regimens combining CTLA-4 blockade with an anti-PD-1/PD-L1 agent led to more frequent, severe, and earlier presentation of dermatologic toxicity.[136]

Maculopapular rash, with or without pruritus, is the most common presentation. Vitiligo is also a fairly common observation in patients with melanoma on PD-1 inhibitors, typically presenting later in the course of treatment. Observed inflammatory skin conditions reported with ICI therapy include eczematous, lichenoid, and psoriasiform manifestations, as well as bullous dermatitis.[4,133,136,137] Alopecia and hair repigmentation have also been reported.[136,138,139] The majority of dermatologic irAEs are low grade and manageable with appropriate care without requiring interruption of ICI. However, rare cases of severe cutaneous reactions such as Stevens-Johnson syndrome/toxic epidermal necrolysis and drug rash with eosinophilia and systemic symptoms have been reported.[137,140,141] Although serious conditions typically required hospitalization, resolution was achievable via systemic immunosuppressive therapy and ICI discontinuation.

GI Toxicity

GI irAEs may present as diarrhea or symptoms of colitis, which include watery diarrhea, cramping, and urgency. Diarrhea and colitis are the second-most commonly reported AEs with ICIs, and symptoms typically develop within 6 to 8 weeks of starting treatment.[142,143] GI irAEs have been reported more frequently with anti-CTLA-4 monotherapy than with PD-1/PD-L1 inhibitors. In studies of CTLA-4 blockade, diarrhea has been reported in up to half of patients, with incidence typically reported between 30% and 40%.[29,144] The highest rates of ICI-mediated GI irAEs have been seen with the addition of a PD-1/PD-L1 inhibitor to CTLA-4 blockade.[145–147] Retrospective case

Ocular Toxicity



[a] Patients experiencing ocular adverse events (AEs) may present with any of the following symptoms: blurred/distorted vision, blind spots, change in color vision, photophobia, tenderness/pain, eyelid swelling, proptosis. Episcleritis can be associated with red or purple discoloration of the eye. Uveitis can be associated with eye redness.

[b] Treat blepharitis per the episcleritis algorithm.
[c] See Principles of Immunosuppression (IMMUNO-A, available online, in these guidelines, at NCCN.org).
[d] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[e] Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[f] If refractory to high-dose systemic steroids, consider adding infliximab or antimetabolites (eg methotrexate) for pan-uveitis.

ICI_EYE-1

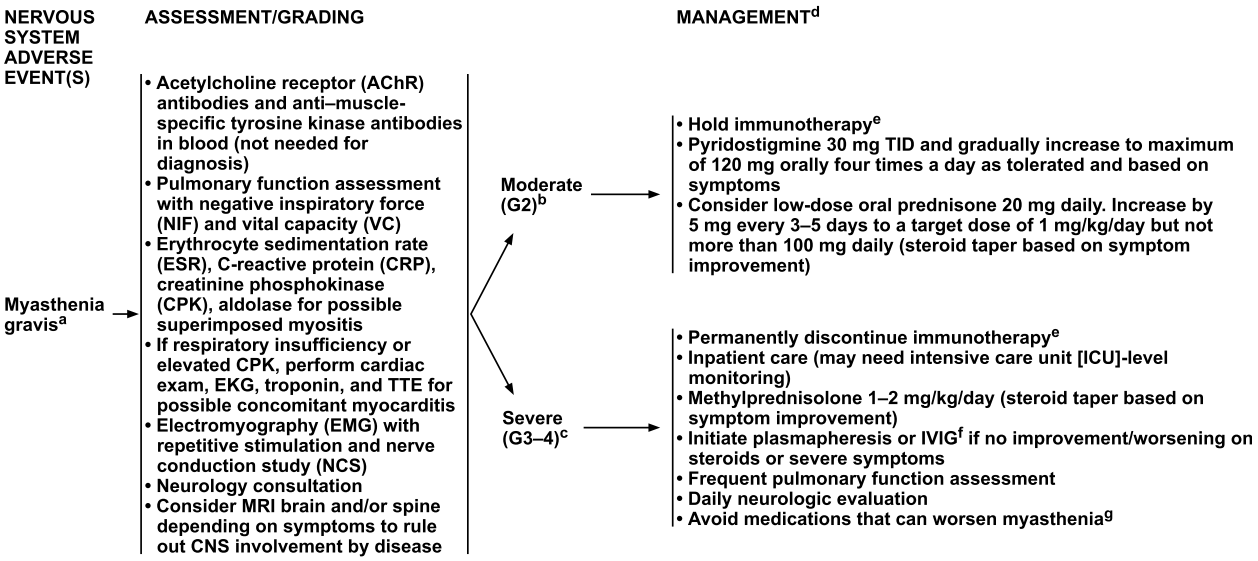
reviews suggest that symptom grade may not correlate with colitis severity as seen by endoscopy and histology.[66,148]

Systematic reviews and meta-analyses have examined the incidence of specific GI irAEs in patients with solid tumors who received ICI therapy. A meta-analysis of 34 studies enrolling 8,863 patients with solid tumors examined the incidence of GI irAEs with various ICIs.[147] The highest rates of GI irAEs were seen in patients receiving combination ipilimumab plus nivolumab, with all-grade colitis, severe colitis, and severe diarrhea reported in 13.6%, 9.4%, and 9.2% of patients, respectively. Incidence of irAEs with ipilimumab monotherapy was 9.1% for all-grade colitis, 6.8% for severe colitis, and 7.9% for severe diarrhea. Monotherapy with a PD-1/PD-L1 inhibitor had the lowest GI irAE incidence, with 1.3% for all-grade colitis, 0.9% for severe colitis, and 1.2% for severe diarrhea. No significant differences in GI irAE incidence were observed by tumor type (eg, melanoma, NSCLC, RCC).[147] Another meta-analysis compared the pooled incidence of diarrhea and colitis for different checkpoint inhibitors in patients with melanoma (CTLA-4, n=3,116; PD-1 inhibitors, n=1,537). PD-1 inhibitors were associated with a lower relative risk of all-grade diarrhea and colitis compared with anti–CTLA-4 agents, whereas combination therapy was associated with a higher relative risk of diarrhea and colitis than monotherapy. Rates of discontinuation were higher among patients taking anti–CTLA-4 agents.[146]

Corticosteroids are typically the first line of treatment of GI irAEs. In retrospective reviews of patients with ICI-related enterocolitis, symptoms resolved with corticosteroid treatment in approximately 40% to 60% of individuals.[143,148,149] However, a recent retrospective analysis of patients found higher infection rates among patients treated with long-duration steroids (>30 days). Long-duration corticosteroid without infliximab was associated with increased infection risk compared with short-duration steroid plus infliximab, suggesting that earlier nonsteroid immunosuppressive therapy may confer better outcomes.[66]

Endoscopy revealed colonic ulcerations more commonly in steroid-refractory cases.[143,148,149] Case studies report on the successful use of infliximab for treating severe, steroid-refractory colitis associated with ipilimumab.[149–151]

Nervous System Toxicity



[a] Progressive or fluctuating muscle weakness, generally proximal to distal. May have bulbar involvement (ie, ptosis, extraocular movement abnormalities resulting in double vision, dysphagia, facial muscle weakness) and/or respiratory muscle weakness. May occur with myositis and myocarditis. Respiratory symptoms may require evaluation to rule out pneumonitis. Miller Fisher variant of Guillain-Barré syndrome (GBS) has overlapping symptoms (ophthalmoplegia and ascending weakness).
[b] Some symptoms interfering with ADLs. Myasthenia Gravis Foundation of America (MGFA) severity class I (ocular symptoms and findings only) and MGFA severity class II (mild generalized weakness).
[c] Limiting self-care and aids warranted, weakness limiting walking, any dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms or MGFA severity class III-IV moderate to severe generalized weakness to myasthenic crisis.
[d] See Principles of Immunosuppression (IMMUNO-A, available online, in these guidelines, at NCCN.org).
[e] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[f] Total dosing should be 2 g/kg, administered in divided doses per package insert.
[g] Beta-blockers, ciprofloxacin, and IV magnesium.

ICI_NEURO-1

Case series and reports have also documented successful treatment of ICI-mediated, steroid-dependent, or steroid-refractory enterocolitis with vedolizumab.[76,152] Vedolizumab may be effective in the setting of infliximab-resistant inflammation of the small intestine and colon.[77]

Hepatic Toxicity

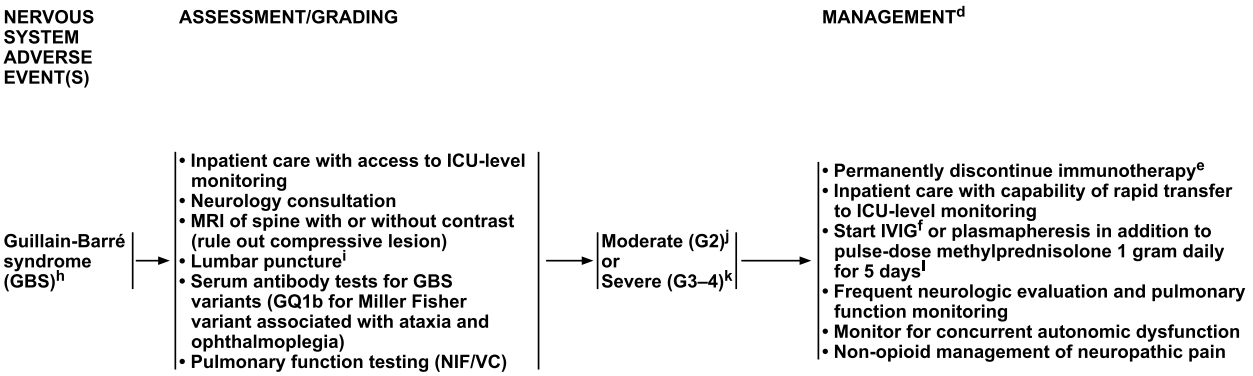
Although immune-related hepatotoxicity occurs at a lower rate than diarrhea/colitis, it is a well-documented ICI-mediated irAE that is typically mild but can be severe or even fatal in rare cases.[18] Asymptomatic elevations in AST and alanine transaminase are the most commonly observed hepatic AEs.[10,135] The pooled incidence of immune-related hepatotoxicity is estimated at 3% to 9% for ipilimumab and between 0.7% and 1.8% for PD-1/PD-L1 inhibitors.[153] Combination therapy is associated with a considerably higher incidence of hepatotoxicity with 29% and 17% experiencing any-grade and high-grade hepatotoxicity, respectively.[153,154] Median time of onset is typically 5 to 6 weeks from start of treatment, but irAEs can occur months later.[153,155–157] Autoimmune hepatitis and drug-induced hepatitis can present in a similar fashion and be difficult to distinguish, but can often be differentiated by distinct histologic features and imaging.[158,159] A recent study characterized the distinct histologic patterns associated with hepatitis mediated by CTLA-4 versus PD-1/PD-L1 blockade.[155]

Corticosteroids are the most common method of treatment in most studies of ICI-mediated hepatotoxicity.[153,155,156] In several cases, reinitiation of steroids after taper was needed based on worsening liver values.[156] Mycophenolate has been used to treat severe persistent hepatitis despite corticosteroid therapy.[91,153,160,161] Another study reported the use of cyclosporine as an additional immunosuppressant in the setting of steroid-refractory hepatotoxicity.[156] Infliximab is not recommended given concerns for liver toxicity, although it has not been tested in this setting. Case report data also suggest that tacrolimus may be effective for treating refractory ICI-related hepatitis.[162,163]

Pancreatic Toxicity

Amylase and/or lipase elevations, although typically asymptomatic, can occur with ICI therapy. The potential

Nervous System Toxicity



[d] See Principles of Immunosuppression (IMMUNO-A, available online, in these guidelines, at NCCN.org).
[f] Total dosing should be 2 g/kg, administered in divided doses per package insert.
[h] Progressive, most often symmetrical muscle weakness with absent or reduced deep tendon reflexes. May involve extremities, facial, respiratory, and bulbar & oculomotor nerves. May have dysregulation of autonomic nerves. Often starts with pain in lower back and thighs.
[i] Cerebrospinal fluid (CSF) typically has elevated protein and often elevated white blood cell (WBC) count; even though this is not typically seen in classical GBS, cytology should be sent with any CSF sample.
[j] Some interference with ADLs, symptoms concerning to patient.
[k] Limiting self-care and aids warranted, weakness limiting walking, any dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms.
[l] Steroids are not usually recommended for idiopathic GBS; however, in immunotherapy-related forms, a trial is reasonable in addition to IVIG or plasmapheresis.

ICI_NEURO-2

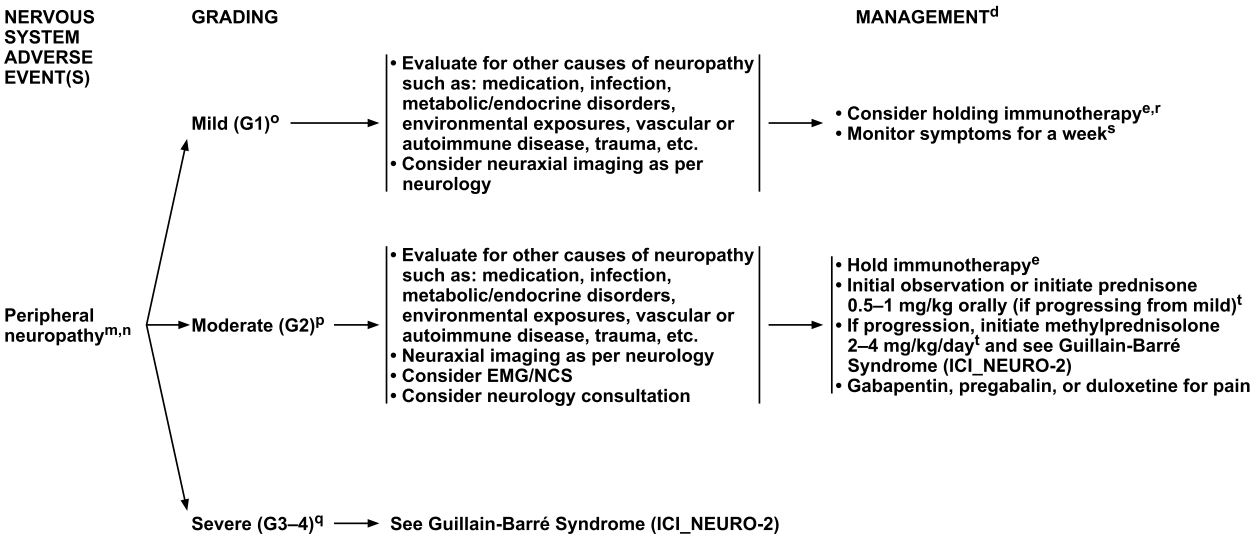
significance of asymptomatic elevations remains unclear, but discontinuation of therapy is not usually recommended based on these findings alone.[29,135,164] Although rare, acute pancreatitis has been observed in patients taking ICIs,[135,158,165] and radiologic features of immune-related pancreatitis have been described.[166] Cases of recurrent pancreatitis have been reported on resumption of PD-1 inhibitors after a hold for initial irAE.[119] Toxic effects on the endocrine pancreas, such as hyperglycemia and diabetes, are addressed in the larger context of the endocrine system in the next section.

Endocrine Toxicity

ICI-related endocrine gland autoimmunity has resulted in dysfunction of the thyroid, pituitary, adrenal glands, and pancreas. Manifestations of immune-mediated endocrine gland dysfunction include hypothyroidism, hyperthyroidism, hypophysitis, type I diabetes, and primary adrenal insufficiency. The mechanisms of ICI-mediated endocrinopathies have been reviewed by Sznol et al[167] and Byun et al.[168] Because many symptoms of endocrine toxicity could be related to other acute illnesses or underlying malignancy, diagnosis can be challenging. Additionally, clinicians have to differentiate whether the source of endocrine dysfunction is central (ie, pituitary) or primary (eg, adrenal or thyroid) to tailor management appropriately.[167,168] Due to this potential complexity, endocrinology specialists play an important role in the management of these irAEs, particularly for severe or complex cases. Alessandrino et al[169] reviewed imaging features of endocrine irAEs at presentation and after treatment to assist in making a differential diagnosis.

Different patterns of endocrine dysfunction have been seen with various ICI regimens. Hypophysitis is characteristic of ipilimumab, whereas thyroid dysfunction is seen more commonly with PD-1/PD-L1 inhibitors. Other types of endocrine irAEs such as primary adrenal insufficiency and type I diabetes are considerably more rare. Overall, combination ICI therapy was associated with highest incidence of endocrinopathy.[1,167,168,170] Median time to onset of moderate to severe endocrinopathy has ranged between 1.75 and 5 months for ipilimumab. Median time to onset of endocrinopathy with PD-1 inhibitor monotherapy ranged from 1.4 to 4.9 months.[142,168]

Nervous System Toxicity



[d] See Principles of Immunosuppression (IMMUNO-A, available online, in these guidelines, at NCCN.org).
[e] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[m] Can present as asymmetric or symmetric sensory-motor deficit. Sensory deficit may be painful or painless parasthesias or potentially life-threatening autonomic (eg, myenteric plexus) dysfunction. Hypo- or areflexia. Isolated sensory deficit or sensory plus lower motor neuron deficit.
[n] GI tract paresis due to myenteric neuritis is a rare toxicity associated with ICI therapy. The presentation may be fulminant with profound ileus. Early institution of high-dose steroids in concert with multidisciplinary management is recommended.
[o] No interference with function and symptoms not concerning to patient. Note: any cranial nerve problem should be managed as moderate.
[p] Some interference with ADLs, symptoms concerning to patient (ie, pain but no weakness or gait limitation).
[q] Limiting self-care and aids warranted, weakness limiting walking or respiratory problems (ie, leg weakness, foot drop, rapidly ascending sensory changes). Severe peripheral neuropathy is not necessarily GBS but the management can be similar.
[r] There is a low threshold to hold immune checkpoint inhibitors in mild cases of peripheral neuropathy.
[s] Specifically monitor for new interference with iADLs from either pain or weakness, gait difficulty, ataxia, or autonomic changes.
[t] Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.

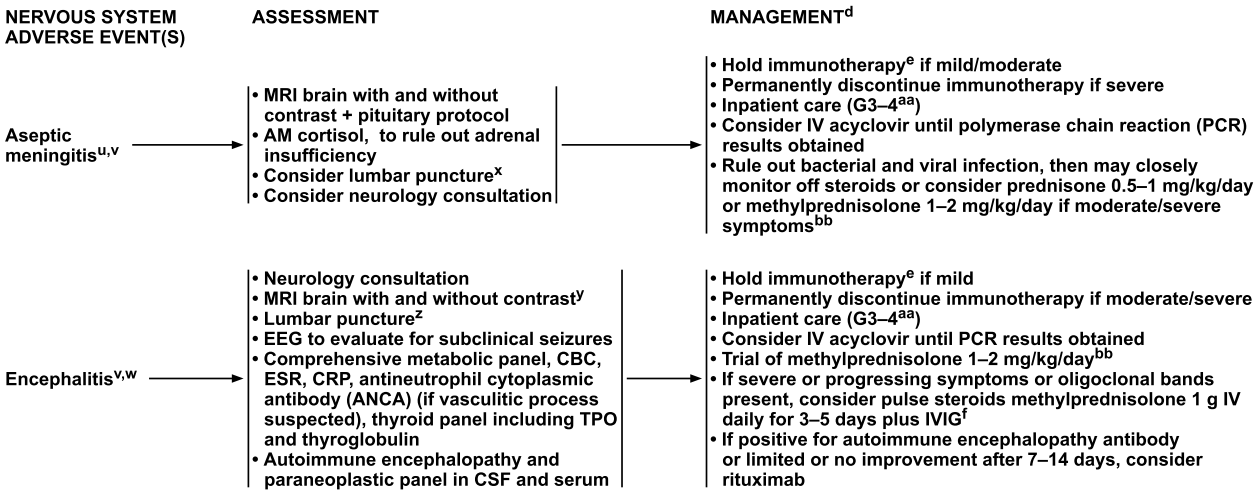
ICI_NEURO-3

A 2018 meta-analysis examined the incidence of endocrine dysfunction across 38 randomized trials enrolling 7,551 patients who received monotherapy with PD-1 inhibitor, PD-L1 inhibitor, or CTLA-4 inhibitor; or combination anti-PD-1/CTLA-4 therapy.[170] The estimated incidence of hypothyroidism was 3.8% with ipilimumab and up to 13.2% for combination therapy. Compared with ipilimumab, PD-1 inhibitors were associated with a significantly greater risk of hypothyroidism (OR, 1.89; 95% CI, 1.17–3.05; P=.03). Interestingly, the risk of hyperthyroidism was higher with PD-1 versus PD-L1 inhibitors (OR, 5.36; 95% CI, 2.04–14.08; P=.002). Overall, the observed incidence of hypophysitis was 6.4% for combination therapy; 3.2% for CTLA-4 inhibitors; 0.4% for PD-1 inhibitors; and below 0.1% for PD-L1 inhibitors. Compared with PD-1 monotherapy, hypophysitis was a more common occurrence during ipilimumab monotherapy (OR, 0.29; 95% CI, 0.18–0.49; P<.001) and combination therapy (OR, 2.2; 95% CI, 1.39–3.60; P=.001). The rarer nature of primary adrenal insufficiency and diabetes precluded statistical comparison of endocrine irAE incidence between different ICI regimens.[170]

A retrospective review identified 27 cases of new-onset insulin-dependent diabetes from a population of 2,960 patients that received ICI therapy over 6 years at 2 academic medical centers (0.9% prevalence).[171] All patients who developed or experienced a worsening of diabetes (ie, becoming insulin dependent) had received anti-PD-1/PD-L1 therapy. Median time to onset was 20 weeks after the first ICI cycle; 59% presented with ketoacidosis, 42% had evidence of pancreatitis, and 40% had one or more positive autoantibodies on testing. Additional concurrent irAEs were present among 70% of the individuals with ICI-related diabetes, many of whom experienced other endocrine AEs. Seventy-six percent of the individuals who developed ICI-related diabetes had the HLA-DR4 genotype, a significantly higher frequency than that reported for the general population, suggesting a possible high-risk allele for the development of this irAE.[171] However, further research will be needed.

ICI-mediated endocrine toxicity often results in permanent organ damage and typically requires life-long hormonal supplementation.[168,172–174] To date, evidence does not suggest that high-dose corticosteroid therapy

Nervous System Toxicity



[d] See Principles of Immunosuppression (IMMUNO-A, available online, in these guidelines, at NCCN.org).
[e] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[f] Total dosing should be 2 g/kg, administered in divided doses per package insert.
[t] Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[u] May present with headache, photophobia, and neck stiffness, often afebrile but may be febrile. There may be nausea/vomiting. Mental status should be normal (distinguishes from encephalitis).
[v] Exclude infectious causes, especially viral (ie, HSV).
[w] Confusion, altered behavior, headaches, seizures, short-term memory loss, depressed level of consciousness, focal weakness, and speech abnormality.
[x] Measure opening pressure and check cell count, protein glucose, gram stain, culture, PCR for HSV and other viral PCRs depending on suspicion and cytology. May see elevated WBC with normal glucose, normal culture, and gram stain. May see reactive lymphocytes or histiocytes on cytology.
[y] May reveal T2/FLAIR changes typical of what is seen in autoimmune encephalopathies or limbic encephalitis or may be normal.
[z] Check cell count, protein glucose, gram stain, culture, PCR for HSV, and other viral PCRs depending on suspicion, cytology, oligoclonal bands, and autoimmune encephalopathy panel. May see elevated WBC with lymphocytic predominance and/or elevated protein.
[aa] Limiting self-care and aids warranted.
[bb] Taper steroids rapidly once symptoms resolve.

ICI_NEURO-4

mitigates organ damage in most cases of ICI-mediated endocrinopathy; however, corticosteroids may help to mitigate symptoms of acute inflammation in the setting of hypophysitis, adrenalitis, or in some cases, thyrotoxicosis. Experts generally do not recommend corticosteroid therapy for managing hypothyroidism or type I diabetes.[167,168,172,174,175]

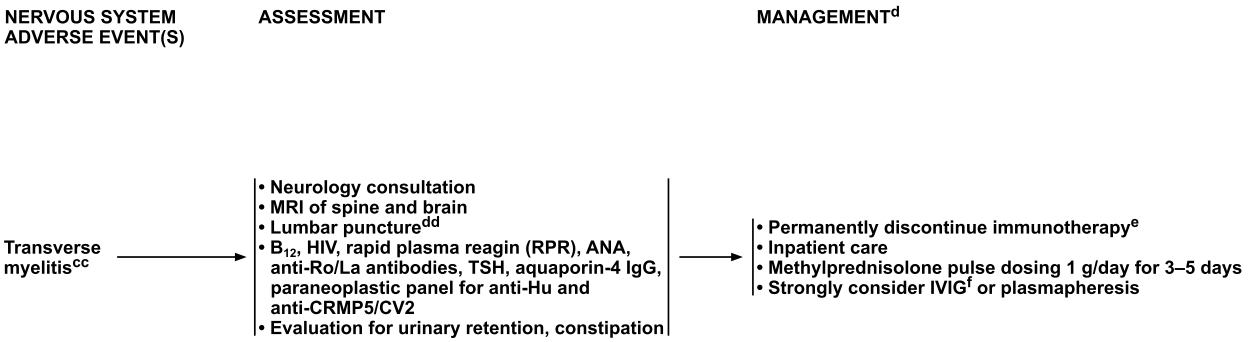
Pulmonary Toxicity

Pneumonitis has been associated with ICI therapy. Generally, rates of any-grade pneumonitis for PD-1/PD-L1 monotherapy have been reported at or below 5% for all-grade, and around 1% for high-grade pneumonitis.[176,177] Unlike the pattern with most other irAEs, ipilimumab monotherapy has a lower incidence of pneumonitis compared with PD-1/PD-L1 inhibitors, with reported rates of less than 1%.[178,179] Observed rates for combination immunotherapy (PD-1/PD-L1 inhibitor plus anti-CTLA-4) are higher than for monotherapy with other ICIs.[176,177,180] Although wide-ranging, median time to irAE onset from start of treatment has been reported at 2.5 months, with generally earlier onset for combination versus monotherapy.[176,180]

A 2016 meta-analysis of 20 clinical trials of PD-1 inhibitors that enrolled 4,496 patients with melanoma, lung, or renal cancer revealed an overall incidence of all-grade and high-grade pneumonitis of 2.7% and 0.8%, with a higher incidence in NSCLC than melanoma.[177] Incidence was higher for combination therapy than for monotherapy (all-grade, 6.6% vs 1.6%; $P<.001$; high-grade, 1.5% vs 0.2%; $P=.001$).

A pooled analysis of 916 patients analyzed pneumonitis among patients who received PD-1/PD-L1 inhibitors with or without anti–CTLA-4 therapy. Incidence of pneumonitis for PD-1/PD-L1 inhibitor monotherapy versus combination therapy (PD-1/PD-L1 inhibitor + CTLA-4 inhibitor) was 3% versus 10%, respectively ($P=.001$). No significant differences were observed in rates of pneumonitis between PD-1 and PD-L1 inhibitors. A similar incidence of pneumonitis was seen among the largest disease cohorts, melanoma and NSCLC, for both monotherapy and combination therapy. Of the patients diagnosed with pneumonitis in this study, most with low-grade cases were treated in the outpatient setting, but 19% of patients with G2 pneumonitis and all patients

Nervous System Toxicity



[d] See Principles of Immunosuppression (IMMUNO-A, available online, in these guidelines, at NCCN.org).
[e] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[f] Total dosing should be 2 g/kg, administered in divided doses per package insert.
[cc] Acute or subacute weakness or sensory changes bilaterally, often with increased deep tendon reflexes.
[dd] Cell count, protein, glucose, oligoclonal bands, viral PCRs, cytology, and onconeural antibodies.

ICI_NEURO-5

with ≥G3 required inpatient care. All mild pneumonitis (G1) cases were managed using ICI dose holds or oral corticosteroid, and all patients with moderate and severe cases received oral or intravenous corticosteroid. Among patients with G3 or higher pneumonitis, 42% required additional immunosuppression with infliximab alone or infliximab with cyclophosphamide.[176]

Renal Toxicity

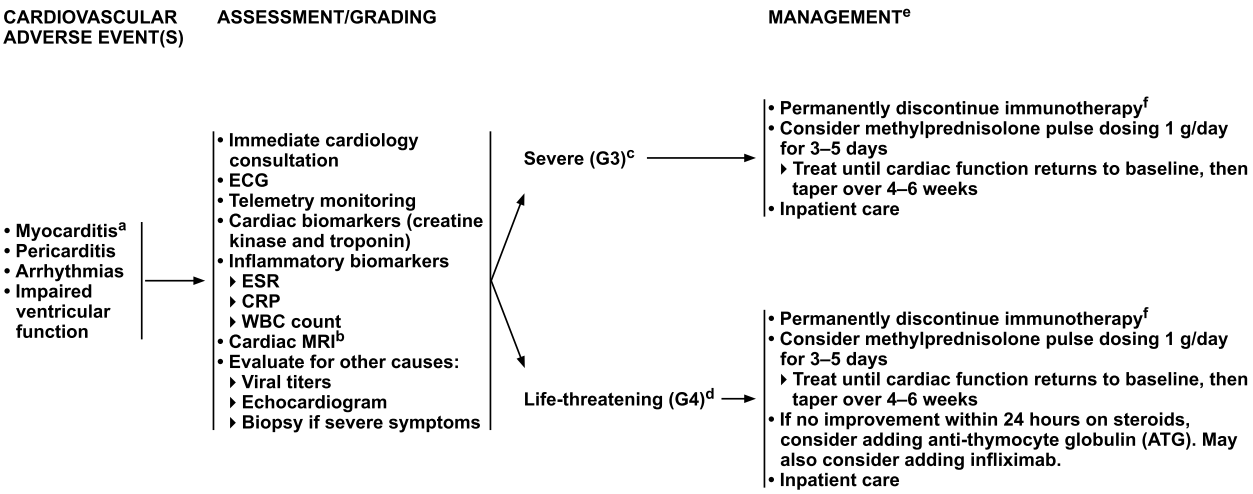
Based on initial studies, the estimated incidence of all-grade renal toxicity is approximately 2% for monotherapy and up to 4.9% for ICI combination therapy.[154,181] Based on a review of phase II and III clinical trials of ICIs enrolling 3,695 patients, the incidence of high-grade renal toxicity was 0.6%.[181] However, reviews of emerging data suggest that incidence of renal toxicity could be considerably higher.[182,183] For ipilimumab, time to onset of renal toxicity has been reported to be around 6 to 12 weeks for ipilimumab, but 3 to 12 months for PD-1 inhibitors.[184]

In the largest case series to date, time to onset of renal toxicity was around 3 months from start of ICI therapy, but varied from 3 weeks to approximately 8 months.[181] Within the cohort of 13 patients, kidney injury was preceded by an extrarenal irAE in 7 patients and pyuria (>5 white blood cells per high-power field) was present in 8 of 13 patients. Pathology revealed acute tubulointerstitial nephritis in 12 of 13 patients. Among the 10 patients who were treated with corticosteroid, 9 showed recovery of renal function (complete recovery in 2, partial recovery in 7). Four patients required hemodialysis, and 2 remained dialysis-dependent.[181] Other case reports/series have discussed similar approaches to diagnosis and management of ICI-related nephritis.[185–187] Notably, there is conflicting evidence surrounding the efficacy of corticosteroid therapy for treating acute interstitial nephritis linked to non-ICI–related causes.[188,189]

Ocular Toxicity

Ophthalmic irAEs are categorized by the affected area of the eye, into ocular inflammation (eg, uveitis, episcleritis, blepharitis, peripheral ulcerative keratitis), orbital inflammation/orbitopathy (eg, idiopathic or thyroid-induced orbitopathy), retinal/choroidal disease (eg, retinopathy or choroidal neovascularization), and optic

Cardiovascular Toxicity



[a] Myocarditis symptoms are nonspecific. It is rare, but potentially severe, not viral in etiology, associated with myositis/myasthenia gravis, and is more common with combination therapy. In fatal cases, conduction abnormalities were mode of death and ejection fraction was preserved.
[b] No evidence specific to immunotherapy-related myocarditis; recommendations drawn from other causes of myocarditis.
[c] Arrhythmia, significant echo findings without hypotension, cardiac markers >ULN.
[d] Arrhythmia, hemodynamic (hypotension/cardiomyopathy) >3xULN.
[e] See Principles of Immunosuppression (IMMUNO-A, available online, in these guidelines, at NCCN.org).
[f] See Principles of Immunotherapy Rechallenge (IMMUNO-C).

ICI_CARDIO-1

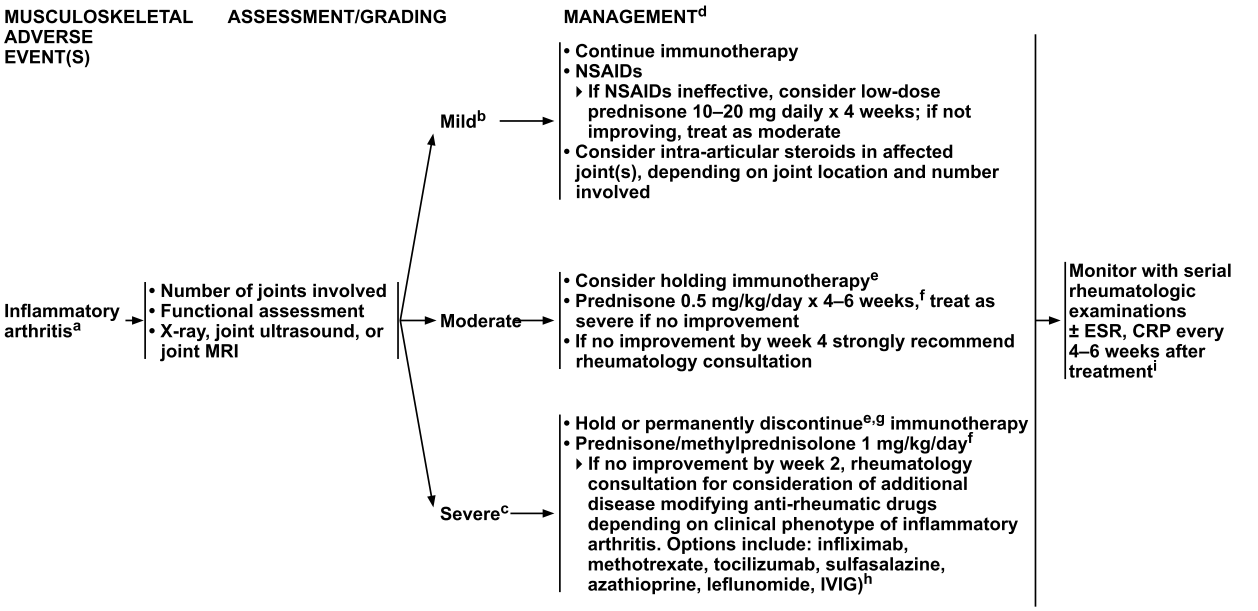
neuropathy.[190–192] Dry eye and uveitis have been the most commonly reported ocular ICI-associated events, with a reported incidence between 1% and 24%.[192–194] Based on case series and reports, mild ophthalmic irAEs have generally been managed successfully using a topical steroid, whereas more severe conditions have required systemic corticosteroid therapy and discontinuation of ICI therapy.[191,192,195,196] Close cooperation with ophthalmologic specialists is critical for prompt diagnosis and optimal treatment.[191,194]

Nervous System Toxicity

ICI-mediated neurologic toxicity spans a broad spectrum of conditions related to autoimmunity within the central and/or peripheral nervous systems. Some neurologic irAEs can be challenging to diagnose due to nonspecific symptoms, variability in presentation, and the wide range of differential diagnoses to consider.[99,101,197] Documented cases of neurologic irAEs include numerous conditions such as myasthenia gravis, GBS-like syndrome, central and/or peripheral neuropathy, aseptic meningitis, encephalitis, and transverse myelitis. With some exceptions (eg, peripheral neuropathies), irAEs of the nervous system are higher grade events by default. Fatalities have been reported in patients receiving ICI who developed severe neurologic irAEs such as immune-mediated encephalitis, myasthenia gravis/myasthenic syndromes, and acute immune demyelinating polyneuropathy.[99,100,197–201] The neurologic irAEs that most commonly resulted in fatality were encephalitis and myasthenia gravis.[44]

A systematic review of the literature examined data on neurologic AEs from case reports and prospective ICI trials (59 trials, n=9,208).[202] The overall incidence of neurologic irAEs was 3.8% for CTLA-4 inhibitors, 6% with PD-1 inhibitors, and 12% for combination therapy. Headache, encephalopathy, and meningitis were the most commonly reported events; the majority of events were lower grade.[202] Generally, reviews report a ≤1% incidence of high-grade neurologic irAEs across various ICI regimens.[101,200,202] Another study probed a pharmaceutical Global Pharmacovigilance and Epidemiology database for neurologic irAEs reported in patients with advanced melanoma receiving nivolumab with or without ipilimumab (12 trials, n=3,763).[101] Of 3,763 patients,

Musculoskeletal Toxicity



[a] Clinical symptoms: joint pain, joint swelling; inflammatory symptoms: stiffness after inactivity, improvement with heat.
[b] Mild in severity or only 1 joint involved.
[c] Limits ADLs, presence of joint erosions.
[d] See Principles of Immunosuppression (IMMUNO-A, available online, in these guidelines, at NCCN.org).
[e] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[f] Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[g] Consider discontinuing immunotherapy if arthritis worsens, with repeated dosing, to the point where daily activities are limited or patient's quality of life is severely impaired.
[h] Consider co-existence of other irAEs in which choice of immunosuppression may be relevant.
[i] Consider ESR, CRP to monitor response if elevated at the onset of therapy.

ICI_MS-1

35 (0.93%) experienced 43 serious neurologic irAEs over an 8-year period, with neuropathy being the most commonly reported event. Resolution of irAE(s) was documented in 75% of patients (26 of 35).

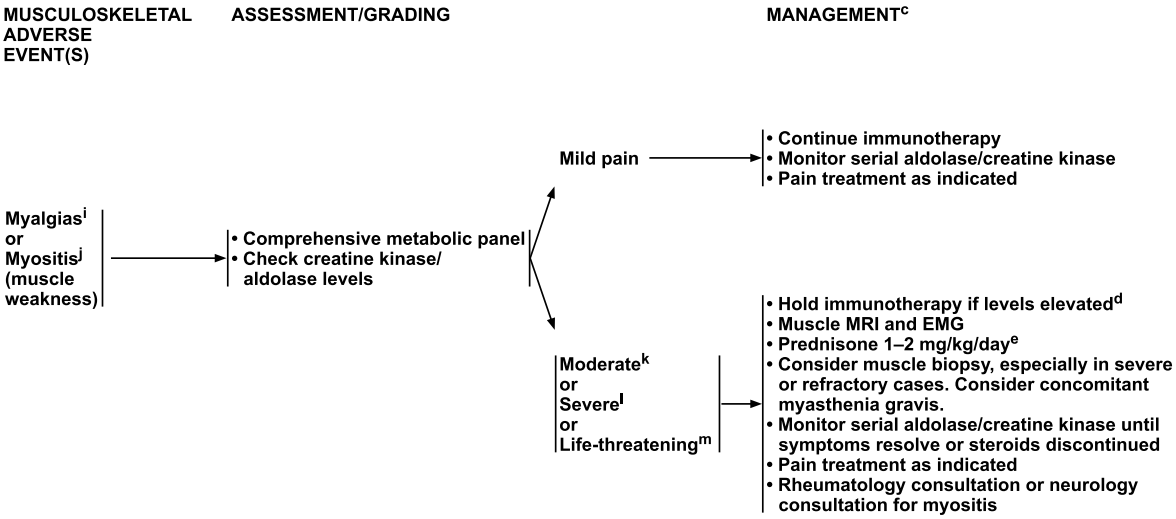
Literature and database reviews generally report a median time to onset of neurologic irAEs of about 6 weeks.[99,101,202] Corticosteroid therapy is usually used as the first line of treatment of neurologic irAEs; high-dose intravenous corticosteroids and ICI discontinuation was used in the setting of higher-grade events.[99,101] Prompt treatment is critical for reducing long-term morbidity and mortality.[68,99,101,197,200] Median time to irAE resolution has been reported at just under 8 weeks.[101] Of note, unlike canonical cases of GBS, ICI-mediated development of GBS-like syndrome has been successfully managed using corticosteroid therapy.[202]

Additional lines of immunosuppressive therapy are often required for cases of rapidly progressive or steroid-refractory neurologic irAEs. Autoimmune encephalitis and other neurologic irAEs have been managed with agents such as IVIG, plasmapheresis, rituximab, and cyclosporine, leading to partial or full recovery.[99,101,199] However, for several reported cases of myasthenic syndrome, encephalitis, or demyelinating polyneuropathy, irAEs proved fatal despite treatment with multiple lines of immunosuppressant (including plasmapheresis, IVIG, tacrolimus, and/or mycophenolate mofetil).[99,100] At present, no definitive outcomes data are available to guide decisions regarding immune-modulating treatments, and clinicians have relied on data from neurologic irAE case reports, management of other autoimmune neurologic disorders, and individual patient characteristics (ie, the presence of irAEs affecting other organ systems).[99]

Cardiovascular Toxicity

Cardiac irAEs are potentially fatal ICI-associated toxicities that have been associated with ipilimumab, pembrolizumab, and nivolumab. Case series reveal a variety of potential manifestations of cardiovascular irAEs, including myocarditis, cardiomyopathy, cardiac fibrosis, heart failure, and cardiac arrest.[20,203,204] Efforts to characterize cardiac irAEs associated with ICI therapy have begun to provide a better understanding of ICI-associated

Musculoskeletal Toxicity



[c] See Principles of Immunosuppression (IMMUNO-A, available online, in these guidelines, at NCCN.org).
[d] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[e] Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[i] Myalgia is a disorder characterized by marked discomfort sensation originating from a muscle or group of muscles.
[j] Myositis is a disorder characterized by inflammation and/or weakness involving the skeletal muscles.
[k] Moderate pain associated with weakness or elevated CK or aldolase; limiting self-care ADLs.
[l] For myalgias, moderate pain associated with weakness; pain limiting iADLs. In myositis, pain associated with severe weakness; limiting self-care ADLs.
[m] Only applies to myositis; urgent intervention indicated.

ICI_MS-2

myocarditis. Data collected over 4 years from 8 sites revealed 35 cases of ICI-mediated myocarditis, which were compared with a sample of patients on ICI therapy without myocarditis.[204] Prevalence was 1.14% in this patient population, with a median onset of 34 days from start of treatment. However, recent evidence suggests that ICI-associated cardiovascular toxicity, myocarditis in particular, is more common than initially thought.[44,204–206]

Recent analysis of the WHO database revealed 101 individual case safety reports of severe myocarditis after initiation of ICI therapy.[206] Of these patients, 57% had received anti PD-1 monotherapy, and 27% received combination PD-1/PD-L1 plus CTLA-4 inhibitor. For patients with available dosing information (n=59), 64% (n=38) had received only 1 or 2 ICI doses at the time of toxicity onset. Concurrent severe irAEs, most commonly myositis and myasthenia gravis, were reported for 42%. Data on cardiovascular comorbidities were not available, but only 25% were on a cardiovascular or diabetes medication regimen.[206]

Based on multicenter registry data, myocarditis was seen more often in patients receiving combination ICI therapy and in patients with diabetes.[204] Approximately half of the patients diagnosed with myocarditis experienced major adverse cardiac events (MACE), which were defined as "the composite of cardiovascular death, cardiogenic shock, cardiac arrest, and hemodynamically significant complete heart block."[204] Troponin levels of ≥1.5 ng/mL were associated with a 4-fold increased risk of MACE (hazard ratio, 4.0; 95% CI, 1.5–10.9; P=.003). Corticosteroid was administered in 89% of cases, with high-dose steroids resulting in better treatment response. Elevated troponin and higher rates of MACE were observed more commonly among patients who were treated with lower-dose corticosteroid.[204]

Pre-existing cardiovascular pathology was identified in most patients (5/8) in one case series.[203] Co-occurrence with noncardiac irAEs was also seen in more than 50% of patients. Corticosteroids and/or supportive care measures were helpful to improve symptoms in most cases, although permanent cardiotoxicity and fatalities also occurred despite intervention.[203] Myositis and myocarditis were seen to co-occur in a recent study of ICI-related fatalities. Notably, myasthenia gravis also co-occurred in 10% of fatal myocarditis cases.[44] Case reports of

PRINCIPLES OF IMMUNOTHERAPY RECHALLENGE

General Principles

- Exercise caution when considering resumption of immunotherapy after significant irAEs. Close follow-up should be performed when resuming immunotherapy to monitor for recurrent symptoms.
  - If re-challenged and toxicity returns, permanently discontinue class of immunotherapy.
  - Assess patient's tumor status prior to rechallenge. If an objective response (complete or partial) to ICI therapy was achieved, resumption of immunotherapy may not be advisable due to risk of toxicity recurrence. Discuss the risks/benefits of restarting immunotherapy with the patient.
- Permanent discontinuation of a given class of immunotherapy is typically warranted in the setting of severe irAEs induced by that class of immunotherapy and may be warranted in the setting of moderate irAEs. For example, if a patient experiences grade 3 or 4 toxicity from an ipilimumab-containing regimen, consideration may be given to later therapy with a PD-1 or PD-L1 monotherapy after resolution of the earlier toxicity.
- With some exceptions, resumption of immunotherapy following grade 2 irAEs can be considered upon resolution to ≤ grade 1.
- Consult with organ-specific specialists prior to resumption of immunotherapy as appropriate following an immunotherapy hold due to irAEs.

Organ-Specific Considerations for Immunotherapy Rechallenge After a Hold

Skin	• Maculopapular rash and/or pruritus: Consider resuming after symptoms have resolved to ≤ grade 1 (ie, once skin condition is mild/localized with only topical intervention indicated). • Permanent discontinuation of immunotherapy in the setting of severe or life-threatening bullous disease (grade 3–4), including all cases of SJS and TEN.
GI	• PD-1/PD-L1 agents: After grade 2–3 colitis, consider resumption of immunotherapy after symptoms have resolved to ≤ grade 1. In rare circumstances in which the patient cannot completely taper off steroids, immunotherapy may be resumed while patient is still on ≤10 mg prednisone equivalent daily. • CTLA-4 agents: Discontinue if irAE is serious or life-threatening. Do not make up doses missed due to irAE and/or required steroid treatment.
Liver	• Transaminitis without elevated bilirubin: following a grade 2 irAE, consider resumption of immunotherapy after ALT/AST return to baseline and steroids, if used, have been tapered to ≤10 mg prednisone equivalent daily. • Permanent discontinuation is warranted in the setting of severe or life-threatening (grade 3–4) hepatitis.
Pancreas	• Symptomatic grade 2 pancreatitis: Consider resumption of immunotherapy if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase. Consider consultation with relevant pancreatic specialist regarding resumption. • Permanent discontinuation is warranted for severe (grade 3–4) pancreatitis.

ICI-related myocarditis have reported irAE flare during steroid taper or ICI rechallenge.[207,208] IVIG was successfully used in a case report of smoldering ICI-related myocarditis that initially responded to corticosteroid but flared on taper.[207]

Musculoskeletal Toxicity

Musculoskeletal and rheumatic irAEs include inflammatory arthritis (IA), myositis, and myalgias. Myositis is characterized by inflammation involving the skeletal muscles, and myalgia involves marked discomfort originating from a muscle or group of muscles. IA is typically identified as a result of joint pain (arthralgia) and/or swelling and stiffness after inactivity. Although rare, severe myositis can be fatal and has been documented more commonly in patients receiving PD-1/PD-L1 inhibitor.[209]

A recent systematic review of the literature examined rheumatic and musculoskeletal irAEs associated with ICI therapy. Data from 33 clinical trials, 3 observational studies, and 16 case reports/series were included.[209] Arthralgia and myalgia were the most commonly reported irAEs, with a widely ranging incidence of 1% to 43%. Five of 33 clinical trials reported cases of arthritis development, and case reports have described IA, vasculitis, myositis, and lupus nephritis. Prospective cohort studies and retrospective reviews report the incidence of IA or other rheumatologic irAEs among patients receiving ICIs to be between 1% and 7%.[67,209–211]

Among a prospective cohort study of 524 patients receiving ICIs, 35 (6.6%) were referred to rheumatology.[67] Twenty patients had IA that presented similar to rheumatoid arthritis (n=7), polymyalgia rheumatica (n=11), or psoriatic arthritis (n=2), while the remaining 15 patients were diagnosed with noninflammatory musculoskeletal conditions. Nineteen patients with IA required low to moderate doses of corticosteroid, and methotrexate was administered in 2 patients. Notably, ICI therapy was not discontinued in these cases.

One case series initially reported on 13 patients (5 receiving nivolumab or ipilimumab monotherapy, 8 receiving combination ICI) who developed new rheumatologic symptoms while receiving an ICI at an academic medical center between 2012 and 2016.[212] Clinical presentation varied, with involvement in both large and small joints of the upper and lower extremities. All patients were treated with corticosteroid therapy, demonstrating variable response. The authors later published

PRINCIPLES OF IMMUNOTHERAPY RECHALLENGE
(continued)

Organ-Specific Considerations for Immunotherapy Rechallenge After a Hold

Endocrine	• Thyroid: No discontinuation required for hypothyroidism. For symptomatic hyperthyroidism resembling Graves-like disease, consider holding immunotherapy and resuming after workup is complete and there is evidence for improvement in symptoms and TFTs. • Primary adrenal insufficiency: After appropriate replacement endocrine therapy is instituted, immunotherapy may continue. • Hypophysitis manifested by deficiency of TSH and/or gonad-stimulating hormones, but without symptomatic pituitary swelling: Immunotherapy may continue while replacement endocrine therapy is regulated. • Hypophysitis accompanied by symptoms of pituitary swelling (eg, headache, vision disturbance, and/or neurologic dysfunction): Hold immunotherapy until resolution of symptoms after steroid therapy; consider resumption of immunotherapy after symptoms related to mass effect are resolved. • T1DM with DKA: Consider resuming once DKA has been corrected and glucose level has stabilized.
Lung	• Progressive grade 1 pneumonitis requiring a hold: Consider resuming upon radiographic evidence of improvement. • Grade 2: Resume once pneumonitis has resolved to ≤ grade 1 and patient is off steroids. • Permanent discontinuation is warranted in the setting of severe (grade 3–4) pneumonitis.
Kidney	• Grade 1–2 renal irAE: Hold immunotherapy per guidelines; upon resolution to ≤ grade 1, consider resuming concomitant with steroid if creatinine is stable. • Permanent discontinuation is warranted in the setting of severe (grade 3–4) proteinuria.
Eye	• Grade 2 irAE: Hold immunotherapy per guideline; consider resumption of immunotherapy in consultation with ophthalmology upon resolution to ≤ grade 1. • Permanent discontinuation of immunotherapy is warranted in the setting of severe (grade 3–4) uveitis or episcleritis.
Nervous System	• Myasthenia gravis: Consider resuming immunotherapy after moderate (grade 2) AE based on steroid responsiveness. Permanently discontinue immunotherapy after grade 3–4 AE. • GBS: Permanently discontinue immunotherapy for any grade GBS. • Peripheral neuropathy: Following hold for grade 1–2 AE, consider resuming if symptoms resolve to ≤ grade 1 or if patient has well-controlled isolated painful sensory neuropathy. • Aseptic meningitis: Consider resuming following mild to moderate AE if symptoms resolve to grade 0. • Encephalitis: Permanent discontinuation is warranted in the setting of moderate to severe encephalitis (grade 2–4). • Transverse myelitis: Discontinuation of immunotherapy following any-grade transverse myelitis.
Cardiovascular	• Grade 1 myocarditis: Consider resuming upon resolution of symptoms. • Permanent discontinuation is warranted in the setting of grade 2–4 myocarditis.
Musculoskeletal	• Inflammatory arthritis (moderate to severe irAE requiring hold): Resume upon stabilization or adequate management of symptoms. Permanent discontinuation may be warranted for severe inflammatory arthritis that significantly impairs ADLs and quality of life.

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2 OF 2

their findings on the distinct clinical presentation of IA within a cumulative series of 30 patients who received various ICI regimens.[213] Patients who received PD-1/PD-L1 inhibitor monotherapy tended to have small joint IA as their sole irAE, whereas patients on a combination regimen (PD-1/CTLA-4 blockade) were more likely to present with knee arthritis, higher levels of C-reactive protein, and prior irAE of another type, and display a reactive arthritis-like phenotype. Ten of 30 patients required additional lines of immunosuppressive therapy beyond corticosteroid (ie, methotrexate or TNF blockers).[213]

Reported cases of IA or other rheumatologic irAEs have generally been responsive to immunosuppressive therapy, with approximately one-quarter to one-third of patients requiring additional lines of therapy beyond corticosteroid.[67,213,214]

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Jeffrey A. Sosman, MD	None	Array Biopharma Inc.; Bristol-Myers Squibb Company; Genentech, Inc.; and Incyte Corporation	None	Hematology/Hematology Oncology
John A. Thompson, MD	Calithera Biosciences; and Celldex Therapeutics, Inc.	AstraZeneca Pharmaceuticals LP; and Boehringer Ingelheim GmbH	None	Medical Oncology, and Hematology/Hematology Oncology
Momen Wahidi, MD	Olympus	None	None	Pulmonary Medicine
Yinghong Wang, MD, PhD	None	None	None	Gastroenterology

The NCCN Guidelines Staff have no conflicts to disclose.

[a]The following individuals have disclosed that they have an employment/governing board, patent, equity, or royalty conflict:
Matthew Frigault, MD: Novartis Pharmaceuticals Corporation