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Release date: March 10, 2020; Expiration date: March 10, 2021

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Management of Immunotherapy-Related Toxicities
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Management of Immunotherapy-Related Toxicities

Disclosure of Relevant Financial Relationships

The NCCN staff listed below discloses no relevant financial relationships:

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Alyse Johnson-Chilla, MS, Guidelines Coordinator, NCCN, has disclosed that she has no relevant financial relationships.

Griselda Zuccarino-Catania, PhD, Oncology Scientist/Medical Writer, NCCN, has disclosed that her spouse is employed by Janssen Pharmaceuticals, Inc.

Anita Engh, PhD, Oncology Scientist/Medical Writer, NCCN, has disclosed that she has no relevant financial relationships.

To view all of the conflicts of interest for the NCCN Guidelines panel, go to NCCN.org/disclosures/guidelinepanellisting.aspx.

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Management of Immunotherapy-Related Toxicities, Version 1.2020

Featured Updates to the NCCN Guidelines

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ABSTRACT

The NCCN Guidelines for Management of Immunotherapy-Related Toxicities provide interdisciplinary guidance on the management of immune-related adverse events (irAEs) resulting from cancer immunotherapy. These NCCN Guidelines Insights describe symptoms that may be caused by an irAE and should trigger further investigation, and summarize the NCCN Management of Immunotherapy-Related Toxicities Panel discussions for the 2020 update to the guidelines regarding immune checkpoint inhibitor–related diarrhea/colitis and cardiovascular irAEs.

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*Provided content development and/or authorship assistance.

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.

PLEASE NOTE

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines Insights highlight important changes in the NCCN Guidelines recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further the understanding of these changes by summarizing salient portions of the panel's discussion, including the literature reviewed.**

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

PRINCIPLES OF ROUTINE MONITORING FOR IMMUNE-CHECKPOINT INHIBITORS

Pre-Therapy 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) • Infectious disease screening as indicated	Clinical exam at each visit with adverse event (AE) symptom assessment	Follow-up testing based on findings, symptoms
Imaging • Cross-sectional 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	Repeat prior to each treatment or every 4 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 CT with contrast or MRCP for suspected pancreatitis.
Thyroid (ICI_ENDO-2) • Thyroid-stimulating hormone (TSH), free thyroxine (T4)[c]	Every 4–6 weeks during immunotherapy, then follow-up every 12 weeks as indicated	Total T3 and free T4 if abnormal thyroid function suspected.
Adrenal/Pituitary (ICI_ENDO-4) • Adrenal: Serum cortisol (morning preferred)[c] • Pituitary: TSH, free thyroxine (T4)[c]	Repeat prior to each treatment or every 4 weeks during immunotherapy, then follow-up every 6–12 weeks	Luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone (males), estradiol (females), 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 with contrast to evaluate for pneumonitis, biopsy if needed to exclude other causes.
Cardiovascular (ICI_CARDIO-1) • Consider baseline EKG • 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. Depending on clinical situation, consider C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), or creatine phosphokinase (CPK)

[a] Prior to initiating treatment, counsel patients and caregivers on the warning signs and symptoms of immune-related adverse events (irAEs). See Principles of Immunotherapy Patient Education (IMMUNO-B).

[b] Closer monitoring may be required for patients with combination immunotherapy regimens. Refer to prescribing information for each individual immunotherapy agent for monitoring recommendations.

[c] After first four doses of immunotherapy, only as clinically indicated.

IMMUNO-1

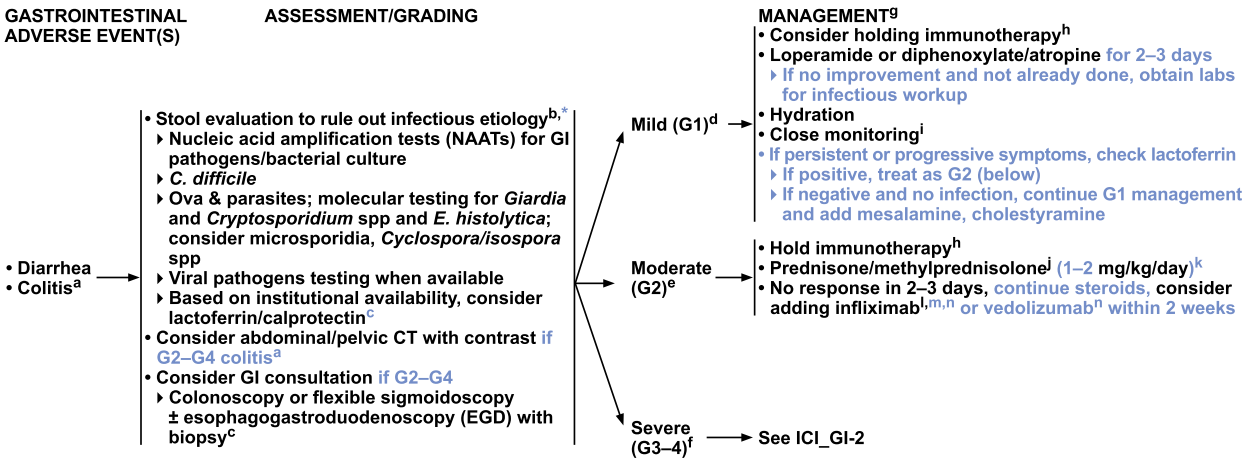
Overview

Immune checkpoints are part of the natural balance of the immune system to prevent autoimmunity and are exploited by cancer cells to suppress the immune response. Immune checkpoint inhibitors (ICIs) block proteins—namely PD-1, PD-L1, and CTLA-4—that allow tumor cells to evade detection and killing by T cells.[1–6] Since the FDA-approval of the CTLA-4 inhibitor ipilimumab in 2011, ICIs have become a treatment option for several advanced cancers. ICIs significantly improve overall survival and delay progression of tumors in patients with a variety of cancers.[7] Indications for ICIs have expanded dramatically and now include a wide array of cancer types.[1–8]

A major drawback of ICI therapy is the potential for immune-related adverse events (irAEs), which can affect any organ or tissue. The pharmacodynamics and pharmacokinetics of ICI immunotherapy differ greatly from those of cytotoxic chemotherapy or targeted anticancer therapy.[9] Traditional cytotoxic chemotherapy often results in acute-onset emetic and myelosuppressive effects, whereas irAEs tend to be relatively delayed in onset and inflammatory or autoimmune in nature.[10–13] 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 subsequent uncontrolled activation of immune effector cells. 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. Later-onset irAEs, which are typically less common, tend to be more-localized, organ-specific reactions. Research is ongoing into the specific mechanisms underlying irAEs associated with specific ICIs. The reported incidence of any-grade irAEs associated with single-agent ICI treatment ranges widely across agents and trials, from approximately 15% to 90%,[14,15] and patterns of toxicity may differ between specific ICI agents.[16] Severe irAEs leading to discontinuation of treatment have occurred in up to 13% of patients receiving anti–PD-1 monotherapy in clinical trials.[17–24] 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.

Recognizing Immune-Related Symptoms

Onset of irAEs can be immediate or delayed by as much as 2 years, and can affect any organ system.[25] Early

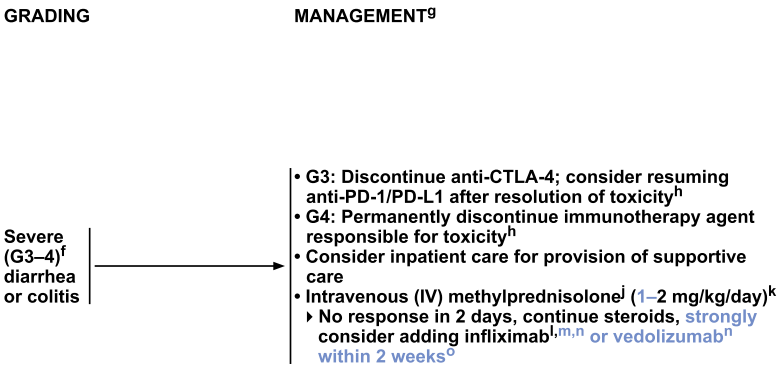


[a] Symptoms include: watery diarrhea, cramping, urgency, abdominal pain, blood and mucus in the stool, fever, nocturnal bowel movements. Blood in the stool and/or fever should prompt a more thorough workup for infection and for other causes of GI bleeding, including peptic ulcer disease (PUD) and malignant bleeding.
[b] It is not necessary to wait for test results before providing therapy to manage immune-related adverse events (irAEs).
[c] If positive lactoferrin, strongly recommend early endoscopy or flexible sigmoidoscopy with biopsy within first 2 weeks of the onset of symptoms.
[d] Fewer than 4 bowel movements above baseline per day and no colitis symptoms.
[e] 4–6 bowel movements above baseline per day, colitis symptoms, not interfering with ADLs.
[f] 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).
[g] See Principles of Immunosuppression (IMMUNO-A).
[h] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[i] If progressive, consider stool evaluation to rule out infectious etiology.
[j] Convert to prednisone when appropriate.
[k] Treat until symptoms improve to Grade ≤1 then taper over <4–6 weeks. In cases where infliximab or vedolizumab is used, an attempt to taper steroids in <4 weeks should be made to minimize the complication of infection.
[l] Duration of therapy with tumor necrosis factor alpha (TNF-alpha) blockers or integrin blocker is not clearly defined; evidence supports up to three doses (at weeks 0, 2, and 6) and is associated with reduced recurrence rates. Repeat endoscopy to assess endoscopic healing may be helpful to guide colitis treatment duration, but is optional. See Principles of Immunosuppression (IMMUNO-A).
[m] An FDA-approved biosimilar is an appropriate substitute for infliximab.
[n] Obtain TB test before receiving first dose of infliximab or vedolizumab.Treatment does not need to be held for results.
*Stool evaluation and all sub-bullets were added to the workup for G1.

ICI_GI-1

recognition of symptoms and prompt intervention are key goals for the successful management of immunotherapy-related toxicity. When encountering one or more of these symptoms, asking appropriate questions can help discern whether the patient is experiencing a symptom due to disease progression, an infection, some other condition, or an irAE. Symptoms that may cause clinical suspicion of an irAE include (main symptoms are bold and underlined; associated symptoms are underlined; possible irAE type/diagnoses are in italics):

- **Change in bowel pattern** compared with baseline, especially if it is watery diarrhea, stool contains blood or mucus, or cramping or severe abdominal pain develop, may indicate *colitis*. However, blood in the stools and/or fever may be because of other causes of gastrointestinal bleeding, such as *infection* or *peptic ulcer disease* or *bleeding due to tumor*.
- **Cough** may be due to an upper respiratory infection, but especially if the cough is dry or is coupled with shortness of breath, it could indicate *pneumonitis*.
- **Headaches** can be indicative of brain metastases, but when presenting with fatigue, visual symptoms, nausea, and other symptoms, may be indicative of *hypophysitis* (inflammation of the pituitary).[26–28] Headaches may also be indicative of *meningitis* when coupled with a stiff neck, photophobia, nausea, or fever. Headaches can also be indicative of *encephalitis* if coupled with fever, tiredness, confusion, mood change, memory problems, stiff neck, and other symptoms. Headaches, head pain, and scalp tenderness, may be indicative of *giant cell arteritis*.
- **Nausea** is a common symptom that can accompany certain cancer therapies. Nausea with abdominal pain/bloating could indicate *pancreatitis*. Nausea that occurs during infusion of an ICI, accompanied by fever/chills, hypertension, hypotension, sweating, myalgia, cough, or shortness of breath, may indicate an *infusion-related reaction*.
- **Rashes** are very common and may be accompanied by itching that can lead to scratching and severe *skin toxicities* causing edema, oozing, papulation, excoriations, lichenification, which may indicate *bullous dermatitis*, or separation of the dermis, a sign of *Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN)*.
- **Fatigue** is a common symptom that alone or coupled with weight change, nausea, or other nonspecific symptoms may indicate a *thyroid disorder*,[26] *hypophysitis*, or,



[f] 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).
[g] See Principles of Immunosuppression (IMMUNO-A).
[h] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[k] Treat until symptoms improve to Grade ≤1 then taper over <4–6 weeks. In cases where infliximab or vedolizumab is used, an attempt to taper steroids in <4 weeks should be made to minimize the complication of infection.
[l] Duration of therapy with tumor necrosis factor alpha (TNF-alpha) blockers or integrin blocker is not clearly defined; evidence supports up to three doses (at weeks 0, 2, and 6) and is associated with reduced recurrence rates. Repeat endoscopy to assess endoscopic healing may be helpful to guide colitis treatment duration, but optional. See Principles of Immunosuppression (IMMUNO-A).
[m] An FDA-approved biosimilar is an appropriate substitute for infliximab.
[n] Obtain TB test before receiving first dose of infliximab or vedolizumab.Treatment does not need to be held for results.
[o] Fecal transplantation may be considered for immunosuppressant refractory colitis based on institutional availability and expertise.

ICI_GI-2

rarely, *adrenal insufficiency*.[28] Fatigue with tachycardia, palpitations, increased stool frequency, and other symptoms may be *thyrotoxicosis*.[27] Fatigue accompanied by nausea, chest pain, shortness of breath, arrhythmias, and other potentially nonspecific symptoms may be indicative of *myocarditis*. However, fatigue may also be attributed to depression, an infection, disease progression, a hematologic abnormality, or another condition.

- **Muscle** or **joint pain** may be indicative of *musculoskeletal toxicities*. Muscle pain alone or with fatigue, chest pain, and shortness of breath may be due to a *cardiac toxicity*, because myocarditis may occur concurrently with myositis.[29–32]
- **Muscle weakness** may be indicative of *neurologic toxicities*, such as *Guillain-Barré syndrome*, or, if coupled with vision changes, *myasthenia gravis*. Myasthenia gravis related to immunotherapy may be associated with myositis and myocarditis.[31,33,34]
- **Weight loss** and nausea may be due to disease progression, but may also indicate a *hepatic toxicity* or an *endocrine toxicity*.

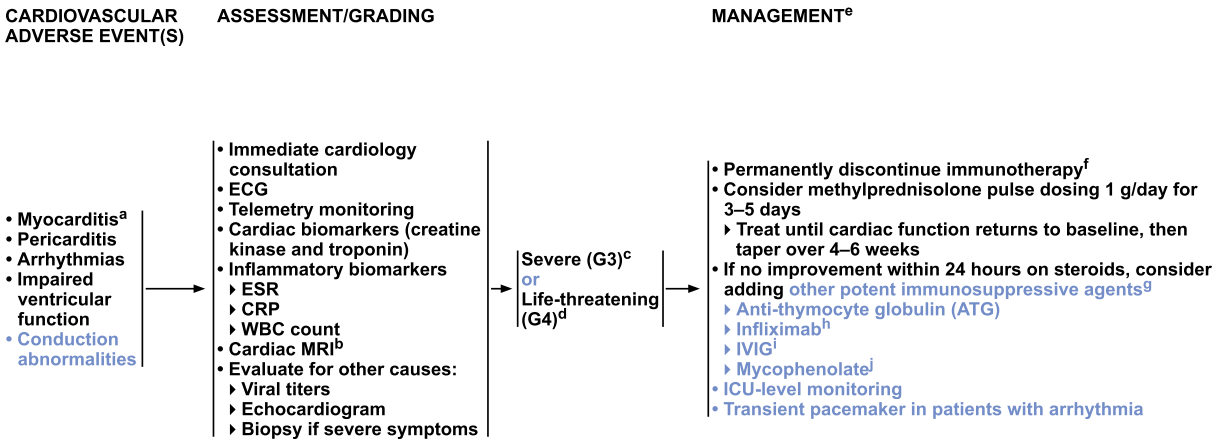
For many patients, routine laboratory monitoring, comparisons to baseline, and targeted questions by the treating healthcare providers will help identify some of the less common but serious irAEs. The primary facets of irAE management include early recognition and grading of toxicity, immunosuppression, and individualized modification to ICI administration. See the complete version of the NCCN Guidelines (available at NCCN.org) for management strategies for these and other ICI-related irAEs updated for 2020.

2020 Updates to the NCCN Guidelines

The NCCN Guidelines for Management of Immunotherapy-Related Toxicities provide guidance on the management of irAEs resulting from cancer immunotherapy, specifically ICI and CAR T-cell therapies. During the meeting to update the guidelines for 2020, the panel discussed updates to the management of many irAEs. These NCCN Guidelines Insights highlight recommendations for the assessment and treatment of ICI-related irAEs related to the gastrointestinal and cardiovascular systems.

Gastrointestinal Adverse Events: Diarrhea/Colitis

The most common gastrointestinal irAE presents as diarrhea and/or symptoms of colitis, which include watery



[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 instability (hypotension/cardiomyopathy), cardiac markers >3xULN.
[e] See Principles of Immunosuppression (IMMUNO-A).
[f] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[g] Successful outcomes have been reported with other immunosuppressive agents, such as alemtuzumab or abatacept.
[h] An FDA-approved biosimilar is an appropriate substitute for infliximab.
[i] Total dosing should be 2 g/kg, administered in divided doses per package insert.
[j] Mycophenolate mofetil treatment (0.5–1 g every 12 hours).

ICI_CARDIO-1

diarrhea, cramping, urgency, abdominal pain, blood or mucus in the stool, fever, or nocturnal bowel movements. Diarrhea and/or colitis are the second most commonly reported AEs with ICIs, and symptoms typically develop within 6 to 8 weeks of starting treatment.[35,36] These gastrointestinal 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%.[14,37] The highest rates of ICI-mediated diarrhea/colitis have been observed with the addition of a PD-1/PD-L1 inhibitor to CTLA-4 blockade.[38–40]

Detection, Initial Assessment, and Grading of Diarrhea/Colitis

To facilitate early detection of diarrhea/colitis, patient education is key. It is important to determine the patient's baseline bowel habits prior to initiation of immunotherapy. Patients are encouraged to report changes in their bowel habits to the treatment team in order to facilitate early detection of colitis that may occur before the next scheduled clinic visit (see IMMUNO-1, page 232). Most cases present as diarrhea (increased frequency of bowel movements), but as described earlier, a variety of other colitis symptoms often occur. Severity of the diarrhea (ie, increase in number bowel movements per day compared with baseline) and the presence and severity of other colitis symptoms determine the grade of the gastrointestinal irAE (Table 1). Hemodynamic instability and life-threatening complications (eg, ischemic bowel, perforation, toxic mega-colon) may be associated with high-grade gastrointestinal irAEs. Table 1 shows grading for these adverse events, based on elements from CTCAE version 5.0 (colitis, enterocolitis, diarrhea),[41] Brahmer et al,[42] and additions from the NCCN Panel (see ICI_GI-1 footnotes, page 233).

Stool evaluation to rule out infectious etiology, specifically *Clostridium difficile,* ova, parasites, and viral pathogens, is an important element of workup for patients with suspected immunotherapy-related diarrhea and/or colitis. For patients presenting with grade 1 diarrhea (increase of <4 bowel movements per day above baseline) and no symptoms of colitis, some panel members defer stool testing until diarrhea has persisted and not improved with conservative treatment (loperamide or diphenoxylate for 2–3 days), or symptoms

Table 1. Grading[a] for Colitis/Diarrhea[b]

	Terms **Diarrhea:** increase in frequency and/or loose or watery bowel movements **Colitis:** inflammation of the colon **Enterocolitis:** inflammation of the small and large intestines
Grade 1	• Increase of <4 bowel movements per day above baseline • Mild increase in ostomy output compared with baseline • No symptoms of colitis (watery diarrhea, cramping, urgency, abdominal pain, blood and mucus in the stool, fever, nocturnal bowel movements)
Grade 2	• Increase of 4–6 bowel movements per day above baseline • Moderate increase in ostomy output compared with baseline • Mild/moderate colitis symptoms: watery diarrhea, cramping, urgency, abdominal pain, blood and mucus in the stool, fever, nocturnal bowel movements • Limiting instrumental ADLs[d]
Grade 3	• Increase of >6 bowel movements per day above baseline • Severe increase in ostomy output compared with baseline • Severe colitis symptoms: watery diarrhea, incontinence, cramping, urgency, abdominal pain, blood and mucus in the stool, fever, ileus, nocturnal bowel movements, peritoneal signs • Limiting self-care ADLs[e] • Hemodynamic instability • Hospitalization indicated

Grade 4	• Same as grade 3, but with:
	  • Other serious/life-threatening complications (eg, ischemic bowel, perforation, toxic mega-colon)
	  • Urgent intervention indicated

Abbreviation: ADLs, activities of daily living.
[a]For all adverse events, grade 5 is defined as death.
[b]Definitions incorporate elements from CTCAE version 5.0 (colitis, enterocolitis, diarrhea),[41] Brahmer et al, 2018,[42] plus additions from the NCCN Panel (ICI_GI-1 footnotes, page 233).
[d]Instrumental ADLs refer to preparing meals, shopping for groceries or clothes, managing money, etc.
[e]Self-care ADLs include bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

have progressed (frequency of bowel movements increased and/or colitis symptoms developed). Blood or mucus in the stools, fever, and/or other symptoms of colitis (watery diarrhea, cramping, urgency, abdominal pain, nocturnal bowel movements) should prompt a thorough workup for infection, including stool evaluation. Patients presenting with blood in the stool should also be evaluated for other causes of gastrointestinal bleeding, including peptic ulcer disease and malignant bleeding, among others (eg, diverticulosis, angiodysplasia, hemorrhoids, ischemia). Diarrhea/colitis associated with immunotherapy can rapidly increase in severity, and therefore therapy to manage these gastrointestinal irAEs can be initiated while awaiting test results.

Measurement of fecal lactoferrin and calprotectin, 2 markers of inflammation, should also be considered as part of initial workup, depending on institutional availability. Calprotectin provides a quantitative measure of inflammation; low levels indicate mild inflammation or normal endoscopy and high levels correlate with ulceration.[43] Fecal lactoferrin is a noninvasive, qualitative biomarker that can predict colitis risk.[44,45]

For patients who present with diarrhea/colitis grade 2 or higher (as defined in Table 1), abdominal/pelvic CT with contrast and gastrointestinal consultation for further evaluation (ie, colonoscopy or flexible sigmoidoscopy ± esophagogastroduodenoscopy [EGD] with biopsy) should be considered. Symptom-based grading (listed in Table 1) may guide prompt initiation of therapy (eg, steroids); however, imaging and biopsy results can help establish the etiology of the problem and assess the likelihood that more aggressive management approaches will be needed. Although retrospective case reviews suggest that symptom grade may not correlate with colitis severity as observed by endoscopy and histology,[46,47] results from a recent retrospective study suggest that lactoferrin results may be used to inform prioritization of endoscopy.[43] This study found that among patients with immune-mediated diarrhea/colitis, lactoferrin levels were strongly correlated with inflammation observed by endoscopy (70% sensitivity), and even more strongly correlated with inflammation detected by histologic evaluation of endoscopy biopsy specimens (90% sensitivity).[43] Histologic findings were correlated with the need for intravenous steroids and/or infliximab/vedolizumab for irAE management.[43] Early endoscopy, defined as ≤7 days after onset of immune-mediated diarrhea/colitis compared with >7 days, was associated with significantly shorter duration of symptoms (47 vs 19 days; P=.026) and shorter steroid treatment duration (49 vs 74 days; P=.053),[43] presumably because earlier endoscopy triggered earlier initiation of management. Performing endoscopy ≤30 days from onset of diarrhea/colitis (vs >30 days) was associated with significantly shorter duration of steroid treatment, a trend toward shorter duration of symptoms, and a significant reduction in recurrence of symptoms (50% vs 21.8% of patients; P=.001). Better outcomes for patients who undergo endoscopy within 30 days of onset may be due to the earlier initiation of infliximab/vedolizumab (15 vs 31 days from onset; P=.030). Given the results of this recent study,[43] early endoscopy with biopsy within the first 2 weeks of the onset of symptoms is strongly recommended for all patients with positive lactoferrin results, even those who have only grade 1 symptoms (per Table 1). Fever and tenderness upon abdominal examination may be an indication of bowel perforation warranting immediate imaging and treatment.

Management of Mild (Grade 1) Events

For patients presenting with mild diarrhea (grade 1, defined as an increase of <4 bowel movements per day) with no other symptoms of colitis (Table 1), the NCCN Guidelines recommend hydration, considering holding immunotherapy, and monitoring the patient closely to determine whether diarrhea is worsening or other

symptoms of colitis develop (see ICI_GI-1, page 233). Loperamide or diphenoxylate/atropine may be used, although some panel members prefer to wait before starting, out of concern about obscuring signs of worsening diarrhea, which may delay initiation of treatment (eg, steroids) that actually reverses underlying immunotherapy-related inflammation, if present. If diarrhea persists or progresses, or no improvement is seen after 2 to 3 days of loperamide or diphenoxylate/atropine, tests for infections workup should be obtained and levels of fecal lactoferrin should be checked if not already done. Cases of grade 1 diarrhea (increase of <4 bowel movements per day) with no other symptoms of colitis, documented absence of infection, and a negative lactoferrin result, may be managed conservatively (hydration and loperamide or diphenoxylate/atropine), with the addition of mesalamine or cholestyramine, if necessary. If lactoferrin results are positive, however, endoscopy should be strongly considered, if not already performed, even if the only symptom is grade 1 diarrhea. Patients with a positive lactoferrin result and persistent/progressive diarrhea should be treated as those with moderate (grade 2) diarrhea/colitis (see next section), because these cases are likely to require more aggressive management, even if the diarrhea has not yet reached the grade 2 threshold (increase of ≥4 bowel movements per day above baseline) and no other colitis symptoms have yet developed.

Tools for Management of Grade 2 or Higher Events

Corticosteroids are typically the first line of treatment of diarrhea/colitis of grade 2 or higher. In retrospective reviews of patients with ICI-related diarrhea/colitis, symptoms resolved with corticosteroid treatment in approximately half of individuals.[36,46,48] However, for some cases, corticosteroids fail to control symptoms and the diarrhea/colitis may persist or worsen and become life-threatening in the absence of more aggressive management.

Infliximab is a monoclonal anti–tumor necrosis factor alpha (TNF-α) antibody used for treating various autoimmune diseases, including Crohn's disease, ulcerative colitis, rheumatoid and psoriatic arthritis, and psoriasis.[49–51] Infliximab has become a commonly used agent for treating steroid-refractory irAEs that develop during ICI therapy.[25,52] Case studies report on the successful use of infliximab for treating severe, steroid-refractory colitis associated with ipilimumab.[48,53,54] An FDA-approved biosimilar is an appropriate substitute for infliximab.

Vedolizumab is an integrin antagonist that binds to α4β7 integrin, blocking its interaction with mucosal addressin cell adhesion molecule-1 (MAdCAM-1), inhibiting the migration of T cells across the endothelium into inflamed gastrointestinal tissues. Vedolizumab is currently indicated for treating gastrointestinal inflammation due to ulcerative colitis and Crohn's disease.[55,56] Case reports have described the use of vedolizumab for the treatment of ICI-induced diarrhea/colitis.[56–58] Vedolizumab binds to gut homing lymphocytes and may provide more specific immune suppression for the inflamed gastrointestinal mucosa, thereby theoretically avoiding suppression of antitumor immune responses.

Introduction of either infliximab or vedolizumab within 10 days of onset of colitis can reduce the duration of symptoms and improve steroid taper success.[59] Treatment with ≥3 doses of infliximab or vedolizumab, and achieving endoscopic or histologic remission are associated with lower risk of colitis relapse. This is important because endoscopic remission is often a better predictor of a cure than clinical remission, in which cases repeat endoscopy may be helpful.

Case studies suggest that transplantation of fecal microbiota from healthy donors may resolve cases of diarrhea/colitis that are resistant to corticosteroids, infliximab, and vedolizumab.[60]

Management of Moderate (Grade 2) Diarrhea/Colitis

For moderate diarrhea/colitis (grade 2), defined as an increase of 4 to 6 bowel movements per day above baseline and/or mild to moderate symptoms of colitis (as detailed in Table 1), the NCCN Guidelines recommend holding immunotherapy and administering prednisone/methylprednisolone (1–2 mg/kg/d) (see ICI_GI-1, page 233). If no improvement is noted within 2 to 3 days of starting steroid treatment, the NCCN Guidelines recommend continuing steroids and considering adding infliximab (or FDA-approved biosimilar) or vedolizumab, preferably within 2 weeks from onset of diarrhea. A tuberculosis test (blood test preferred) should be obtained before administering the first dose of infliximab or vedolizumab, although treatment can be initiated before results are received.

Management of Severe (Grade 3–4) Events

For severe diarrhea/colitis (grade 3–4), defined as an increase of >6 bowel movements per day above baseline and/or severe symptoms of colitis (Table 1), inpatient care should be considered if needed to provide adequate supportive care (see ICI_GI-2, page 234). Intravenous methylprednisolone, 1 to 2 mg/kg/d, should be administered. After improvement in diarrhea/colitis is noted, the steroid dose may be tapered, usually over 4 to 6 weeks (see later discussion). For diarrhea/colitis related to ipilimumab, the NCCN panel recommends permanent discontinuation if serious or life-threatening diarrhea/colitis occurs. For diarrhea/colitis associated with PD-1/PD-L1 inhibitors, therapy should be held for grade 3, with consideration of rechallenge upon resolution of symptoms

below grade 1. The immunotherapy agent(s) responsible for immune-related grade 4 diarrhea/colitis should be permanently discontinued.

If no improvement is noted within 2 to 3 days on intravenous methylprednisolone (1–2 mg/kg/d), the NCCN Guidelines recommend continuing steroids and strongly considering adding infliximab (or FDA-approved biosimilar) or vedolizumab, preferably within 2 weeks of onset, especially for patients with high-risk endoscopic features.[43] Fecal transplantation may be considered for colitis refractory to immunosuppressant therapy, based on institutional availability and expertise.[60]

Duration of Treatment of Immune-Related Diarrhea/Colitis

For disease monitoring after receiving colitis treatment, checking the levels of calprotectin provides a quantitative measure of inflammation; low levels indicate mild inflammation or normal endoscopy and high levels correlate with ulceration.[43] Repeat endoscopy to assess endoscopic healing may be helpful to guide colitis treatment duration, but is optional. Endoscopy has revealed colonic ulcerations more commonly in steroid-refractory cases.[36,46,48]

Retrospective analysis of patients with refractory diarrhea/colitis 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.[47] If a systemic corticosteroid is given, treatment should be continued until symptoms improve to grade 1 or better, then dose tapered over 4 to 6 weeks. In cases in which infliximab or vedolizumab is used, a shorter taper may help minimize the complication of infection, provided that the diarrhea/colitis (or other concomitant irAEs) does not worsen during the taper. Intravenous methylprednisolone should be converted to oral prednisone when appropriate.

The duration of therapy with TNF-α blocker (infliximab) or integrin blocker (vedolizumab) is not clearly defined. Evidence supports the use of up to 3 doses (at weeks 0, 2, and 6) to reduce risk of recurrence and increase likelihood of endoscopic/histologic remission.[59]

Cardiovascular Adverse Events

Efforts to characterize cardiac irAEs associated with ICI therapy have begun to provide a better understanding of ICI-associated myocarditis. Case series reveal a variety of potential manifestations of cardiovascular irAEs, including myocarditis, pericarditis, arrhythmias, cardiomyopathy, cardiac fibrosis, heart failure, and cardiac arrest.[61–65] 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.[62] Prevalence was 1.14% in this patient population, with a median onset of 34 days from initiation of treatment. However, recent evidence suggests that ICI-associated cardiovascular toxicity, myocarditis in particular, is more common than initially thought.[33,34,62,66]

Myocarditis symptoms are nonspecific, such as myalgia, shortness of breath, and chest pain, which could also be attributed to pneumonitis or other irAEs.[29] It is rare, but potentially severe, associated with myositis/myasthenia gravis, and is more common with anti–CTLA-4/anti–PD-(L)1 combination therapy. A recent report analyzed a total of 40 case reports describing cardiac irAEs and found that even with rapid assessment and initiation of immunosuppression, mortality was still high at 23%.[67] In fatal cases, conduction abnormalities were the mode of death and ejection fraction was preserved.

Cardiac irAEs have been associated with ipilimumab, pembrolizumab, and nivolumab. Based on multicenter registry data, myocarditis was observed more often in patients receiving combination ICI therapy and in those with diabetes.[62] Recent analysis of the WHO database revealed 101 individual case safety reports of severe myocarditis following initiation of ICI therapy.[34] Of these cases, 57% had received anti PD-1 monotherapy and 27% received combination PD-1/PD-L1 plus CTLA-4 inhibitor. For cases 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% of cases. Data on cardiovascular comorbidities were not available, but only 25% of patients with myocarditis were on medication to treat cardiovascular disease or diabetes.[34]

Preexisting cardiovascular pathology was identified in more than half of patients (5/8) in one case series.[61] Co-occurrence with noncardiac irAEs was also observed in >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.[61] Myositis and myocarditis were observed to co-occur in a recent study of ICI-related fatalities. Notably, myasthenia gravis also co-occurred in 10% of fatal myocarditis cases.[33] Case reports of ICI-related myocarditis have reported irAE flare during steroid taper or ICI rechallenge.[68,69]

Management

Baseline EKG and individualized assessment in consultation with cardiology should be considered as indicated. Periodic testing should be considered for patients with abnormal baseline or symptoms (see IMMUNO-1, page 232).

Once a cardiac irAE is suspected, immediate cardiology consultation and intensive care unit–level monitoring is recommended (see ICI_CARDIO-1, page 235). Assessment should include telemetry monitoring and electrocardiogram. Recommended laboratory testing includes cardiac biomarkers (creatine kinase and troponin levels) and inflammatory biomarkers (erythrocyte sedimentation rate, C-reactive protein level, and WBC count). To rule out other potential causes, evaluation may include viral titers, echocardiogram, or biopsy in the case of severe symptoms. When feasible, cardiac MRI may provide additional diagnostic information.[70]

Table 2 summarizes grading for cardiovascular adverse events that may be associated with ICI therapy, based on elements from CTCAE version 5.0 (myocarditis, pericarditis, ventricular arrhythmia),[41] Brahmer et al,[42] and additions from the NCCN Panel (see ICI_CARDIO-1 footnotes, page 235). In the setting of severe (grade 3) cardiac irAE, arrhythmia may be accompanied by significant echocardiogram findings without hypotension, and cardiac biomarkers above the upper limit of normal (ULN). Life-threatening (grade 4) cardiac irAEs are denoted by arrhythmia, hemodynamic instability, and cardiac biomarkers >3 times the ULN. Transient pacemaker may be recommended in patients with arrhythmia.[67] Immunotherapy should be permanently discontinued for any grade 3 or 4 cardiovascular irAEs. The panel recommends methylprednisolone pulse dosing (1 g/d for 3–5 days). In a multicenter registry report, corticosteroids were administered in 89% of cases with myocarditis, with high-dose steroids resulting in better treatment response.[62] Elevated troponin and higher rates of major adverse cardiac events, which were defined as "the composite of cardiovascular death, cardiogenic shock, cardiac arrest, and hemodynamically significant complete heart block," were observed more commonly among patients who were treated with lower-dose corticosteroid.[62] The NCCN Panel recommends treating with steroids until cardiac function returns to baseline, then dose taper over 4 to 6 weeks.

Beyond treatment with high-dose steroids, there are few data to suggest the optimal subsequent therapy should steroids fail. Treatment options for both severe (grade 3) or life-threatening cases (grade 4) are the same given the rapid progression of cardiac irAE. If no improvement is noted within 24 hours, the addition of other potent immunosuppressive agents should be considered, such as antithymocyte globulin (ATG),[62,67,71–73] infliximab[61,67,71,74] or an FDA-approved biosimilar, intravenous immunoglobulin (IVIG),[67,73,75] or mycophenolate.[76]

ATG is a polyclonal antibody derived from lymphoid cell immunized horses or rabbits, which reverses immunotoxicity by inducing T-cell depletion. Data supporting use of ATG to treat myocarditis and arrhythmia are limited to a number of single case reports with favorable outcomes.[62,67,71] Infliximab has also been used in cases studies to treat cardiotoxicities,[61,67,71,74] but it is important to note that it is contraindicated for patients who have heart failure.[29,77] IVIG is used to reduce the levels of antibodies that may be causing damage. IVIG was successfully used in a case report of smoldering ICI-related myocarditis that initially responded to corticosteroids but flared upon taper,[68] and has been used for years in the setting of cardiac rejection.[73,75] Mycophenolate mofetil is an antiproliferative agent that is used for cardiac transplant patients.[76]

Two additional immunosuppressive agents may be used based on case studies. A case report of a patient on pembrolizumab with confirmed myositis–myasthenia gravis overlap syndrome with worsening cardiac arrhythmia after methylprednisolone, mycophenolate, plasmapheresis, and rituximab described a successful outcome after treatment with alemtuzumab,[65] a monoclonal antibody that binds to

Table 2. Grading[a] for Select Cardiovascular Events[b]

	Terms
	Myocarditis: inflammation of the muscle tissue of the heart **Pericarditis:** irritation to the layers of the pericardium (the protective sac around the heart) **Other cardiovascular irAEs:** arrhythmias, impaired ventricular function, conduction abnormalities
Grade 1	• Asymptomatic • Abnormal cardiac biomarkers (creatine kinase, troponin) • Abnormal ECG or physical findings (eg, rub) consistent with pericarditis
Grade 2	• Mild symptoms or symptoms with moderate activity or exertion: may include chest pain, myalgia, dyspnea, arrhythmia, palpitations, peripheral edema, pleural effusion, fatigue • Abnormal screening tests: cardiac biomarkers (creatine kinase, troponin), ECG • For arrhythmia: expedited cardiology evaluation indicated
Grade 3	• Symptoms at rest or with minimal activity or exertion, or new onset of symptoms: may include chest pain, myalgia, dyspnea, arrhythmia, palpitations, peripheral edema, pleural effusion, fatigue • Pericarditis with physiologic consequences (eg, pericardial constriction) • Cardiac biomarkers (creatine kinase and troponin) >ULN • Significant echocardiogram findings without hypotension
Grade 4	• Moderate to severe decompensation (worsening signs and symptoms): may include congestive heart failure, chest pain, myalgia, dyspnea on exertion, arrhythmia, palpitations, peripheral edema, pleural effusion, fatigue • Hemodynamic instability (hypotension/cardiomyopathy) • Cardiac biomarkers (creatine kinase and troponin) >3× ULN • Life-threatening • Urgent intervention indicated (eg, continuous intravenous therapy or mechanical hemodynamic support for myocarditis)

Abbreviations: ECG, electrocardiogram; irAEs, immune-related adverse events; ULN, upper limit of normal.
[a]For all adverse events, grade 5 is defined as death.
[b]Cardiovascular events that can be associated with cancer immunotherapy. Definitions incorporate elements from CTCAE version 5.0 (myocarditis, pericarditis, ventricular arrhythmia),[41] Brahmer et al,[42] and additions from the NCCN Panel (see ICI_CARDIO-1 footnotes, page 235).

CD52 on some immune cells and leads to destruction of peripheral immune cells. Similarly, one case reported success using abatacept[78] (a CTLA-4 agonist that affects T cells and may lead to rapid inactivation of the normal immune response) in a patient receiving nivolumab who developed glucocorticoid-refractory myocarditis with concurrent myositis, who had also been treated with plasmapheresis.

Conclusions

Proper management of ICI-related toxicities requires early identification of potential irAEs in order to administer adequate treatment. Recent case studies and clinical experience have changed irAE management strategies, which have been incorporated in the 2020 update of NCCN Guidelines for Management of Immunotherapy-Related Toxicities. These NCCN Guidelines Insights provide context for topics that were discussed by the panel during the 2020 update meeting.

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