National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

# Management of Immunotherapy-Related Toxicities

Version 1.2020 — December 16, 2019

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# NCCN Guidelines Version 1.2020
# Management of Immunotherapy-Related Toxicities

NCCN Guidelines Index
Table of Contents
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# NCCN Guidelines Version 1.2020
# Management of Immunotherapy-Related Toxicities





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

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/member_institutions.aspx.

**NCCN Categories of Evidence and Consensus:** All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

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# NCCN Guidelines Version 1.2020
# Management of Immunotherapy-Related Toxicities

NCCN Guidelines Index
Table of Contents
Discussion

**Updates in Version 1.2020 of the NCCN Guidelines for Management of Immunotherapy-Related Toxicities from Version 2.2019 include:**

## Global Changes

- ICI_FTG-1 is a new page.
- ICI_MS-3 is a new page

## Management of Immune Checkpoint Inhibitor-Related Toxicities

### IMMUNO-1

- Heading of page updated: "Principles of Routine Monitoring *for Immune-Checkpoint Inhibitors*."
- "Baseline Assessment" heading was changed to "Pre-Therapy Assessment"
- "Infectious disease screening as indicated" was moved from General bloodwork to Clinical Pre-Therapy Assessment
- Imaging, first bullet was updated: "~~CT~~ *Cross-sectional* imaging"
- General Bloodwork monitoring frequency was updated: "Repeat ~~every 2–3~~ *prior to each treatment or every 4* weeks..."
- Pancreatic evaluation for abnormal findings/symptoms: "CT with contrast or MRCP" replaced "imaging"
- Thyroid Evaluation for Abnormal Findings
  - "Free T4" was added.
  - "TPO antibodies if TSH is high, TRAbs if TSH is low" was removed.
- Adrenal/Pituitary
  - Pre-Therapy Assessment: "(AM) with ACTH" added to first bullet.
  - Monitoring frequency was updated, "~~Every 2–3~~ *Repeat prior to each treatment or every 4* weeks..."
  - Evaluation for abnormal findings/symptoms updated: "... testosterone *(males), estradiol (females)*..."
- Pulmonary evaluation for abnormal findings/symptoms: "with contrast" was added
- Cardiovascular: "Consider baseline EKG" added to Pre-Therapy Assessment
- Musculoskeletal evaluation for abnormal findings/symptoms: "Depending on clinical situation, consider C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), creatine phosphokinase (CPK)" was added.
- Footnote a was updated: "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).*"
- Footnote c is new: "After first four doses of immunotherapy, only as clinically indicated."

### ICI_INF-1

- The mild and moderate grade infusion-related reaction management were split and extensively revised.

### ICI_DERM-1

- "for pruritus" was added to the 3rd bullet of Mild and Moderate Management
- Moderate Management
  - First bullet updated: "~~Consider holding~~ *Continue* immunotherapy"
  - 4th bullet was updated: "Treatment with *moderate to* high potency topical steroids..."
- Severe Management: "consider biopsy" was added to the 4th bullet

### ICI_DERM-2

- Mild Management: "or lidocaine patches for localized pruritus" was added to the 3rd bullet
- Moderate Management: the 3rd bullet is new, "Consider GABA agonists (gabapentin, pregabalin)"
- Footnote m is new: "If outpatient, consider narrow-band UVB phototherapy."

### ICI_DERM-3

- Recommendations for the assessment/grading and management of bullous dermatitis and SJS/TEN were extensively revised.

### ICI_GI-1

- Assessment/Grading
  - "if G2-G4 colitis" added to 2nd bullet
  - "if G2-G4" added to 3rd bullet
- Management of diarrhea/colitis was extensively revised.

### ICI_GI-3

- Footnote q is new: "Consider initiating steroids while waiting for results in cases of life-threatening transaminitis."

### ICI_GI-5

- Footnote t is new: "Mild symptoms of pancreatitis can include: nausea, bloating, belching, abdominal pain, or back pain."

### ICI_GI-6

- "IV hydration" added to management of mild, moderate, and severe acute pancreatitis
- "Follow-up over time to monitor for pancreatic insufficiency" was added to footnote bb.

Continued

National Comprehensive Cancer Network®

# NCCN Guidelines Version 1.2020
# Management of Immunotherapy-Related Toxicities

NCCN Guidelines Index
Table of Contents
Discussion

**Updates in Version 1.2020 of the NCCN Guidelines for Management of Immunotherapy-Related Toxicities from Version 2.2019 include:**

**ICI_ENDO-1**

- Footnote c is new: "In patients who are critically ill/ill-appearing with sugars >200 mg/dL (typically 300–500 mg/dL), urgent/emergent evaluation for DKA is indicated."
- Footnote d was updated: "The development of type I DM is rare ~~(1%–2%)~~ but can be life-threatening..."

**ICI_ENDO-2**

- Clinical, primary hypothyroidism
  - "free T4" was removed from assessment
  - Management, first sub-bullet was updated: "If TSH is >10, initiate levothyroxine therapy, oral daily ~1.6 mcg/kg or 75–100 mcg *or 50–75 mcg starting dose for elderly patients* with goal of getting TSH to reference range or age-appropriate range. *Repeat TSH in 4–6 weeks to guide dosing changes.*"
- Thyrotoxicosis
  - "if persistent symptoms" added to first sub-bullet under assessment
  - Management, last bullet was updated: "Thyrotoxicosis often evolves to hypothyroidism *(see Clinical, primary hypothyroidism above for levothyroxine dosing)*"

**ICI_ENDO-3**

- Central hypothyroidism and hypophyistis Assessment was updated: "Evaluate *morning* cortisol *and ACTH* ~~(AM)~~, FSH..."
- "Follow free T4 for thyroid replacement in the setting of hypophysitis-induced loss of TSH production" was added to the management of central hypothyroidism and hypophysitis.
- "Follow free T4 for thyroid replacement in the setting of hypophysitis–induced loss of TSH production" was removed from footnote p
- Footnote q was updated: "...Tests may show low ACTH, low morning cortisol, low Na, low K, *and* low testosterone~~, and DHEA-S~~..."
- Footnote r is new: "If a patient has polyuria/polydipsia, consider workup for diabetes insipidus; however, this is exceedingly rare with only a few case reports."
- Footnote s was updated: "... it may also include levothyroxine for central hypothyroidism, ~~and~~ testosterone supplementation in males*, and estrogen in pre-menopausal women if not otherwise contraindicated*..."

**ICI_ENDO-4**

- Assessment/Grading was updated:
  - "Evaluate *morning* cortisol *and ACTH* levels ~~(AM)~~"
  - "renin level" was removed from the 2nd bullet
- Management
  - "and monitor electrolytes" was added to the 4th bullet
  - 3rd sub-bullet was updated: "Fludrocortisone can be started 0.1 mg *daily or* every other day..."
- Footnote u is new: "To rule out central hypothyroidism."

**ICI_PULM-1**

- Management of Moderate Pneumonitis:
  - "Consider" added to 2nd bullet
  - 3rd bullet, 2nd sub-bullet was updated: "Sputum culture, blood culture, and urine ~~culture~~ *antigen test (pneumococcus, legionella)*."
  - 4th bullet was updated: "Consider bronchoscopy with bronchoalveolar lavage (BAL) to rule out infection ~~and malignant lung infiltration~~ *(if feasible, perform bronchoscopy with BAL prior to initiation of treatment to rule out infection)*."
  - "with or without dry cough. Consider infectious etiologies" added to footnote a.
  - "oxygen indicated" added to footnote d.
  - Footnote h is new: "If concern for lymphangitic spread of tumor, biopsy is indicated."

**ICI_PULM-2**

- "Consider PFTs" removed from 4th bullet.
- Footnote j is new: "Options are listed in alphabetical order. There is no data to support the use of one over another."
- Footnote k is new: "An FDA-approved biosimilar is an appropriate substitute for infliximab."
- Footnote l was updated: "Total dosing should be 2 g/kg, administered in divided doses *over 2 to 5 days as* per package insert."

**ICI_RENAL-1**

- Management of Moderate elevated serum creatinine/acute renal failure, "Consider renal biopsy" added to 3rd bullet.
- "PPIs" added to footnote b.
- "(consider vasculitis)" added to footnote c.
- Footnote h is new: "An FDA-approved biosimilar is an appropriate substitute for infliximab."

Continued

National Comprehensive Cancer Network®

# NCCN Guidelines Version 1.2020
# Management of Immunotherapy-Related Toxicities

NCCN Guidelines Index
Table of Contents
Discussion

**Updates in Version 1.2020 of the NCCN Guidelines for Management of Immunotherapy-Related Toxicities from Version 2.2019 include:**

**ICI_EYE-1**
- Management of anterior uveitis, 3rd bullet was updated: "Treatment guided by ophthalmology to include ophthalmic ~~and~~ *with or without* systemic prednisone/methylprednisolone"
- Footnote f was updated: "If refractory to high-dose systemic steroids, consider adding infliximab, *FDA-approved biosimilar,* or antimetabolites..."

**ICI_NEURO-1**
- Assessment/Grading, 3rd bullet updated: "... aldolase*, and anti-striational antibodies* for ~~possible~~ superimposed myositis..."
- Management of Moderate Myasthenia Gravis
  - First bullet updated: "~~Hold~~ *Permanently discontinue* immunotherapy"
  - "Inpatient care" was added.
- Management of Severe Myasthenia Gravis
  - "if no improvement/worsening on steroids or severe symptoms" removed from 4th bullet.
  - 4th bullet, sub-bullet is new: "Consider adding rituximab (375 mg/m$^2$ weekly for 4 treatments or 500 mg/m$^2$ every 2 weeks for 2 doses) if refractory to plasmapheresis or IVIG."
- Footnote f is new: "High-dose steroids (≥2 mg/kg/day) may exacerbate symptoms."

**ICI_NEURO-2**
- Assessment/Grading, 5th bullet was updated: "Serum *ganglioside* antibody tests..."
- Management
  - "then taper over 4 weeks" added to 3rd bullet.
  - Last bullet was updated: "*Gabapentin, pregabalin, or duloxetine for pain* ~~Non-opioid management of neuropathic pain~~"

**ICI_NEURO-4**
- Aseptic meningitis Assessment: "if feasible" added to 3rd bullet.
- Management of Encephalitis: "or plasmapheresis" added to 6th bullet.
- "elevated protein" added to footnote y.
- Footnote cc was updated: "Taper steroids ~~rapidly~~ *over 4 weeks* once symptoms resolve."
- Footnote dd is new: "10 mg/kg IV every 8 hours."

**ICI_NEURO-5**
- Assessment, last bullet was updated: "Evaluation for constipation *and* urinary retention *with bladder scan*."

**ICI_CARDIO-1**
- "Conduction abnormalities" added to Cardiovascular AE list.
- Management of Severe and Life-Threatening were combined and extensively revised.

**ICI_MS-1**
- Footnote h is new: "An FDA-approved biosimilar is an appropriate substitute for infliximab."

**ICI_MS-2**
- Assessment/Grading
  - "and troponin" added to 2nd bullet
  - 3rd and 4th bullets are new
    - "Muscle strength testing"
    - "Consider concomitant myasthenia gravis or myocarditis"
- Management of Mild myalgias or myositis
  - First bullet was updated: "~~Continue~~ *Consider holding* immunotherapy"
  - The 2nd bullet is new: "Consider polymyalgia rheumatica/giant cell arteritis (see ICI_MS-3)"
  - "(eg, NSAIDs)" added to last bullet.
- Management of moderate, severe, or life-threatening myalgias or myositis
  - 4th bullet: "Consider concomitant myasthenia gravis" was removed
  - The last two bullets are new:
    - "Consider IVIG (2 g/kg administered in divided doses per package insert)"
    - "Plasmapheresis, infliximab, or mycophenolate may be considered if refractory to steroids"

Continued

National Comprehensive Cancer Network®

# NCCN Guidelines Version 1.2020
# Management of Immunotherapy-Related Toxicities

NCCN Guidelines Index
Table of Contents
Discussion

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**IMMUNO-A (1 of 3)**
- The name of this page was updated: "Principles of Immunosuppression *for Patients Receiving Immune Checkpoint Inhibitor Immunotherapy*"
- The following bullet was removed from the General Principles: "These immunosuppression recommendations are for patients receiving immune checkpoint inhibitor immunotherapy."
- Prophylaxis
  - Links to the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections were added throughout this section.
  - "Referral to physical therapy and weight-bearing exercises are recommended" added to last bullet.

**IMMUNO-A (2 of 3)**
- Indications for anti-TNFα therapy
  - First bullet, 2nd sub-bullet was updated: "*Additional doses* ~~A second dose~~ of anti-TNFα therapy may be required, and ~~can~~ *should* be administered 2 *and 6* weeks after initial dose of infliximab *or FDA-approved biosimilar*."
  - "(where infliximab is contraindicated)" was added to 2nd bullet, first sub-bullet.

**IMMUNO-B (1 of 3)**
- This page was extensively revised.

**IMMUNO-B (2 of 3)**
- 2nd bullet, 2nd sub-bullet was updated: "Delay in immunotherapy may be *recommended if unclear if irAE is developing or* ~~required~~ until AEs resolve to grade 1 or pre-treatment baseline."

**IMMUNO-B (3 of 3)**
- This page was extensively revised.

**IMMUNO-C (1 of 2)**
- GI, first bullet was updated: "... In rare circumstances in which the patient cannot completely taper off steroids *and symptoms are unresolved*, immunotherapy may be resumed while patient is still on ≤10 mg prednisone equivalent daily. *Consider concurrent vedolizumab upon resumption of PD-1/PD-L1.*"
- Liver, 2nd bullet is new.
- Liver, 3rd bullet, grade 3 hepatitis was removed.

**Management of CAR T-Cell–Related Toxicities**

**CART-1**
- Before and During CAR T-Cell Infusion, 2nd bullet: "clinically significant arrhythmia" was added.
- Post-CAR T-Cell Infusion, 2nd bullet: "or neurotoxicity" was added.

**CART-3**
- Footnote l is new: "GM-CSF is not recommended in the setting of CAR T-cell therapy."

## PRINCIPLES OF ROUTINE MONITORING FOR IMMUNE-CHECKPOINT INHIBITORS

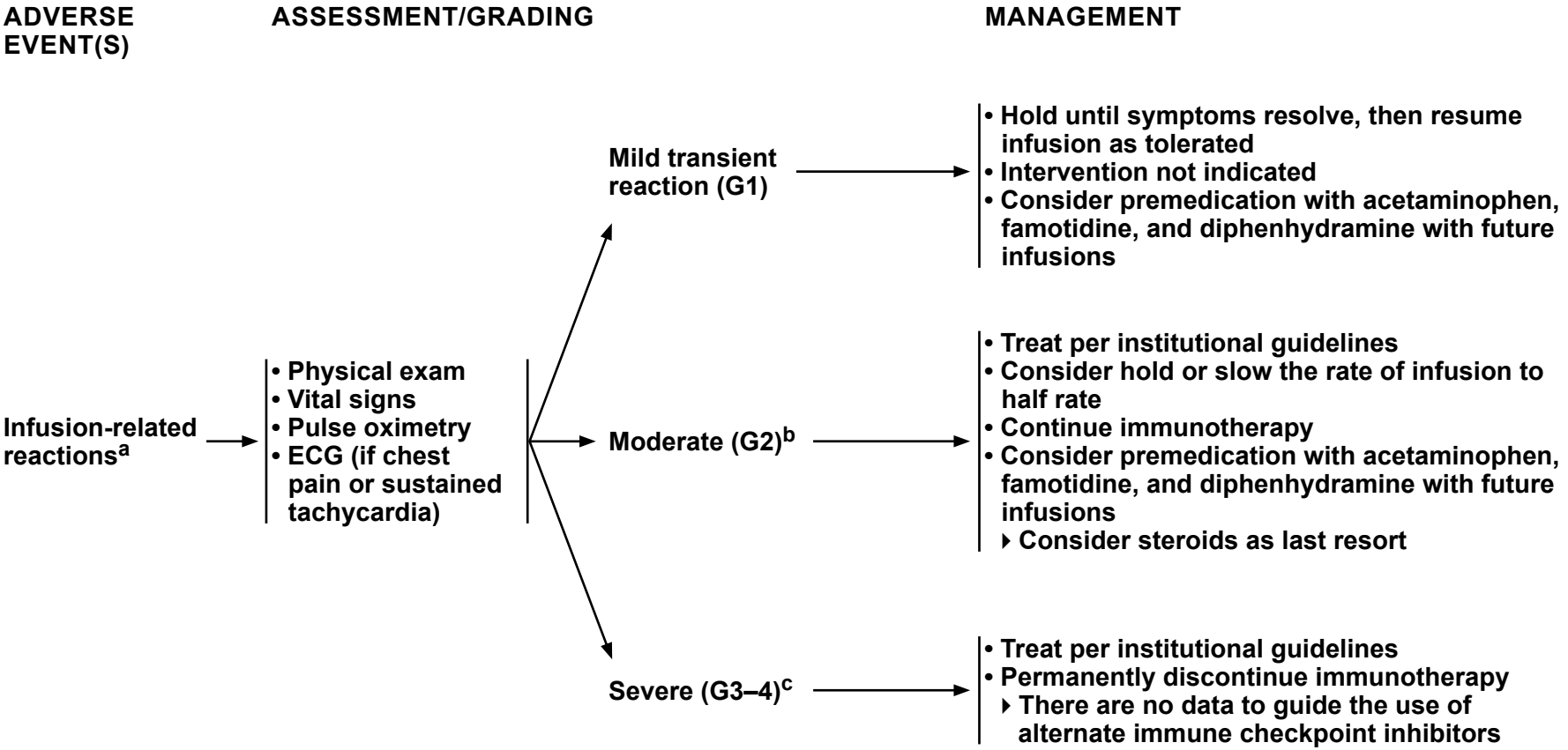
| Pre-Therapy Assessment[a] | Monitoring Frequency[b] | Evaluation for Abnormal Findings/Symptoms |
|---|---|---|
| **Clinical**<br>• Physical examination<br>• Comprehensive patient history of any autoimmune/organ-specific disease, endocrinopathy, or infectious disease<br>• Neurologic examination<br>• Bowel habits (typical frequency/consistency)<br>• Infectious disease screening as indicated | Clinical exam at each visit with adverse event (AE) symptom assessment | Follow-up testing based on findings, symptoms |
| **Imaging**<br>• Cross-sectional imaging<br>• Brain MRI if indicated | Periodic imaging as indicated | Follow-up testing as indicated based on imaging findings |
| **General bloodwork**<br>• CBC with differential<br>• 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)<br>• 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)<br>• 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)<br>• 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)<br>• Adrenal: Serum cortisol (morning preferred)[c]<br>• 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)<br>• Oxygen saturation (resting and with ambulation)<br>• 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)<br>• Consider baseline EKG<br>• 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)<br>• Joint examination/functional assessment as needed for patients with pre-existing disease | No routine monitoring needed if asymptomatic | Consider rheumatology referral.<br>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.

**Note: All recommendations are category 2A unless otherwise indicated.**
**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.**




[a] Symptoms include: Fever/chills/rigors, urticaria/pruritus, angioedema, flushing/headache, hypertension, hypotension, shortness of breath, cough/wheezing, hypoxemia, dizziness/syncope, sweating, and arthralgia/myalgia. Refer to prescribing information for each individual immunotherapy agent for recommendations for premedication to prevent infusion reactions.

[b] Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, acetaminophen, NSAIDs, narcotics, intravenous [IV] fluids); prophylactic medications indicated for less than or equal to 24 hours.

[c] Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement. Hospitalization indicated; life-threatening consequences; urgent intervention.

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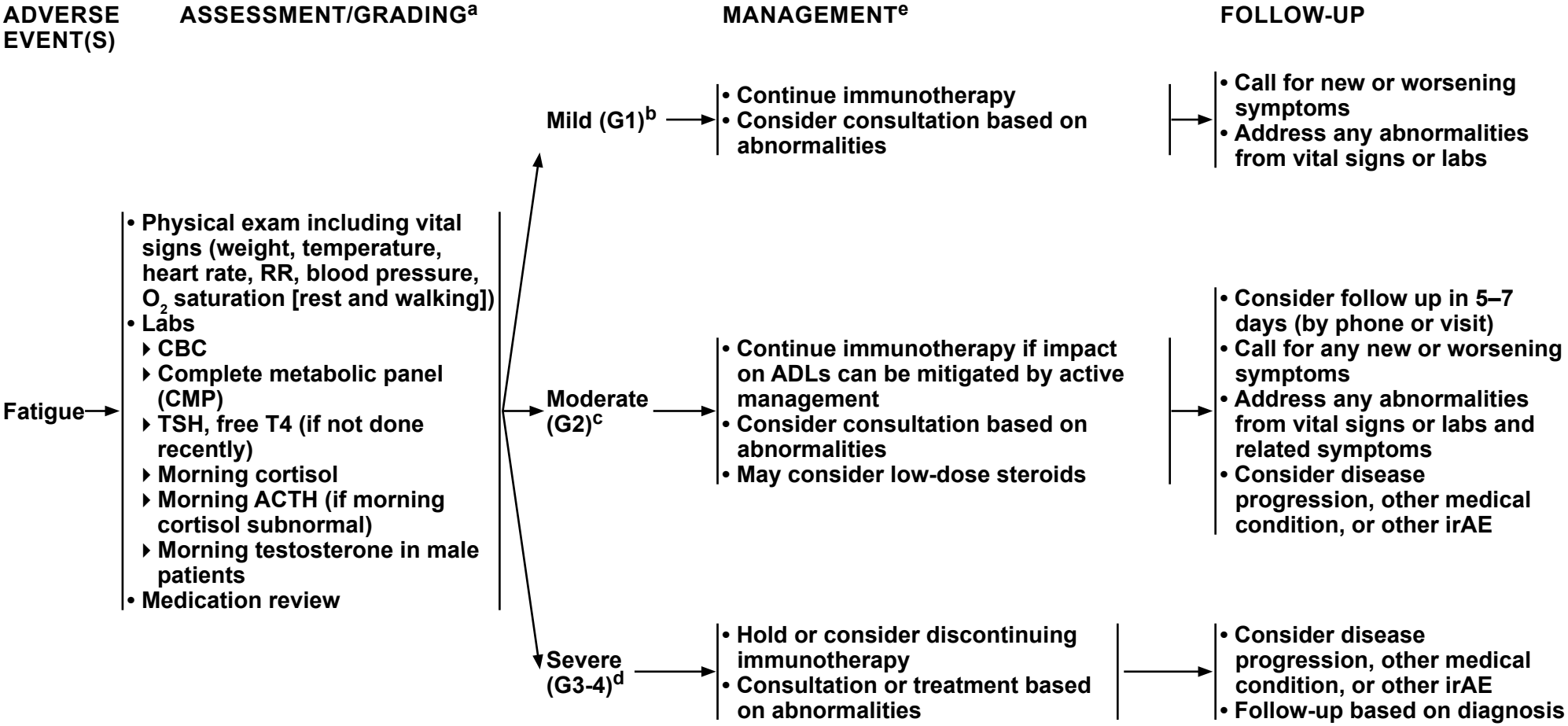


[a] If diagnostic studies indicate central hypothyroidism (ICI_ENDO-3) and/or central/secondary adrenal sufficiency (ICI_ENDO-4), see respective pages for treatment recommendations.
[b] Relieved by rest.
[c] Not relieved by rest; limiting ADLs.
[d] Not relieved by rest, limiting self care.
[e] Based on physical signs and labs, management may include hydration, medication adjustment, education, diet, and sleep hygiene. If symptoms are unrelated to immunotherapy, see NCCN Guidelines for Cancer-Related Fatigue.

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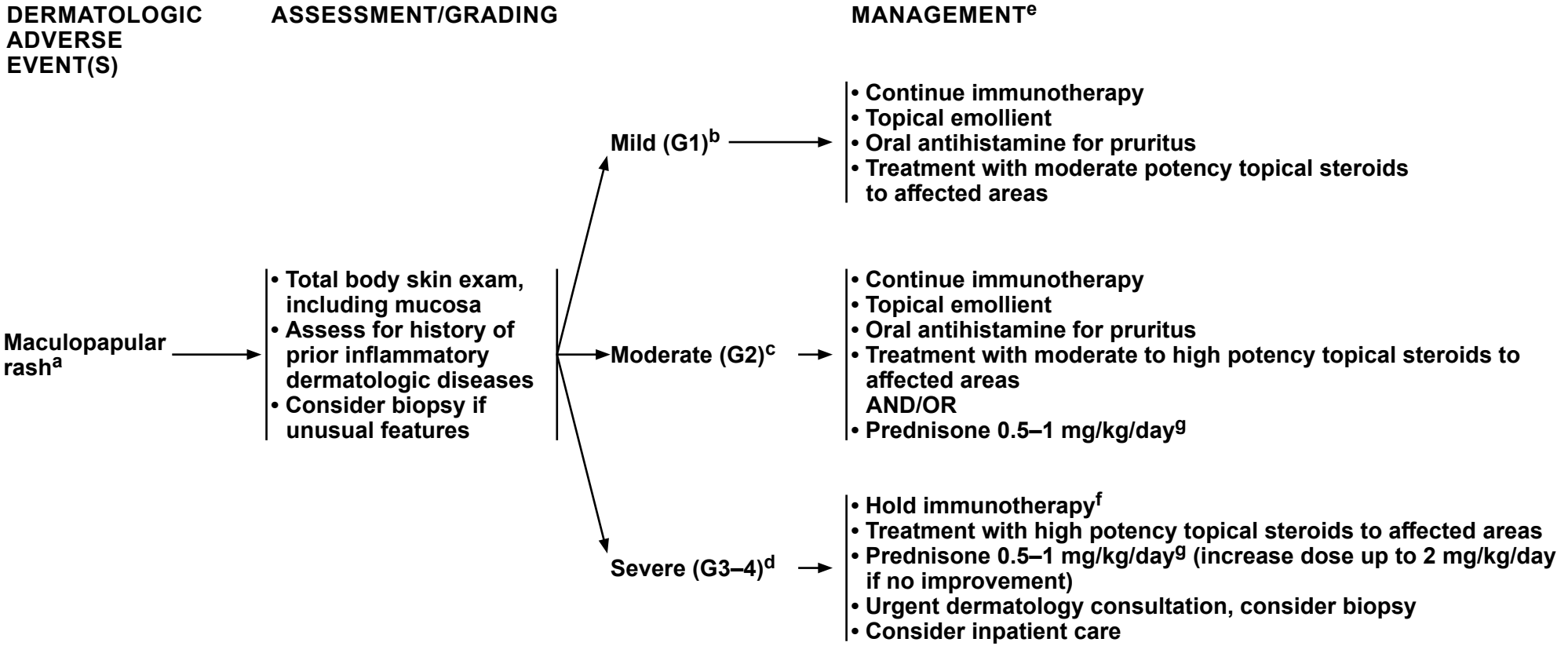


[a] Characterized by the presence of macules (flat) and papules (elevated). Also known as morbilliform rash, it is one of the most common cutaneous adverse events (AEs), frequently affecting the upper trunk, spreading centripetally and may be associated with pruritus.
[b] Macules/papules covering <10% 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).
[f] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[g] Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.

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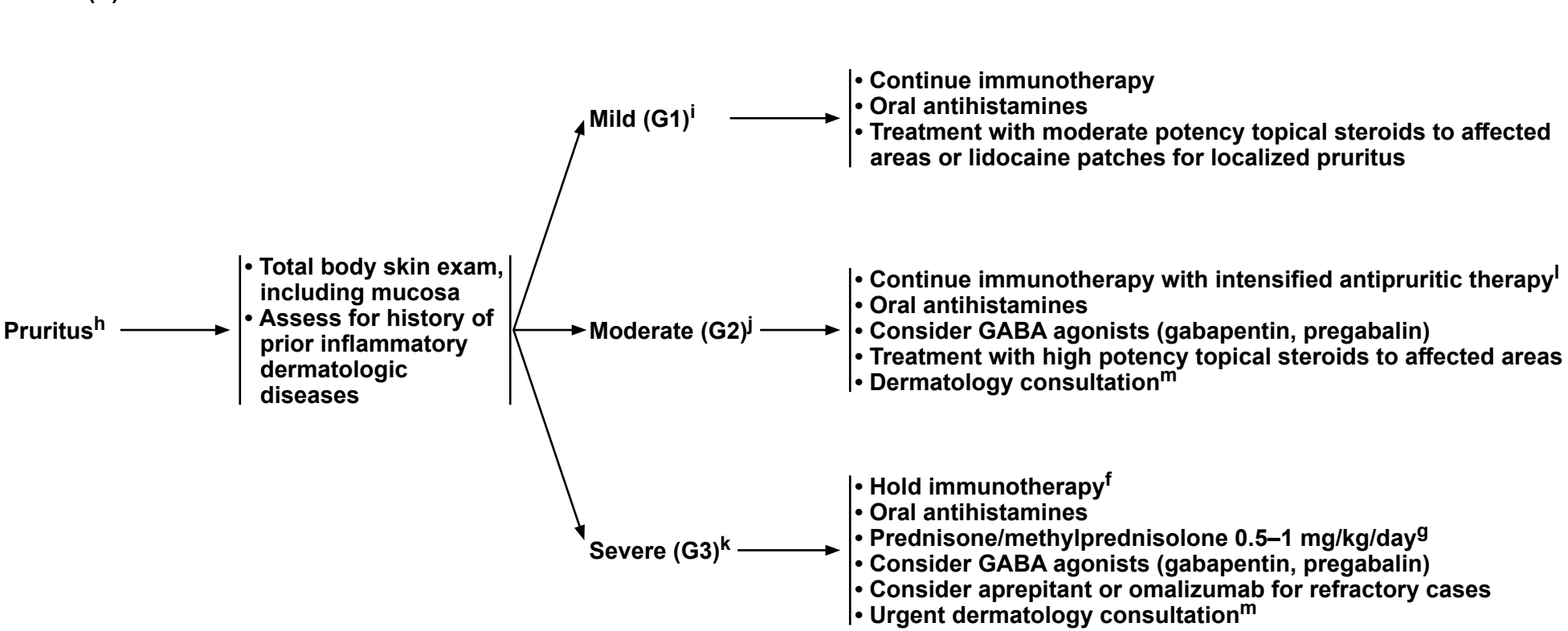


[e] See Principles of Immunosuppression (IMMUNO-A).
[f] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[g] Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[h] Characterized by an intense itching sensation.
[i] Mild or localized.
[j] Intense or widespread; intermittent; skin 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.
[m] If outpatient, consider narrow-band UVB phototherapy.

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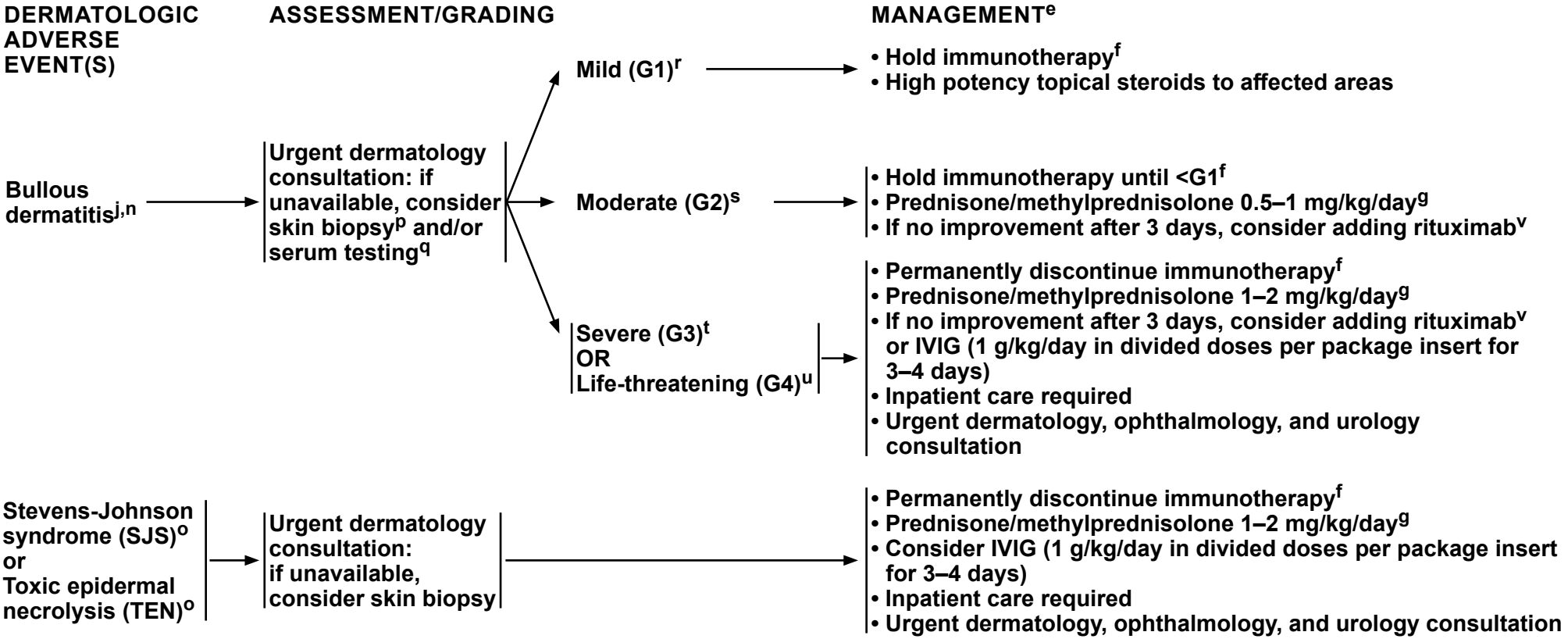


[e] See Principles of Immunosuppression (IMMUNO-A).
[f] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[g] Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[j] Intense or widespread; intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); limiting iADLs.
[n] Characterized by inflammation of the skin and the presence of bullae, which are filled with fluid. The most common irAE reported is bullous pemphigoid.
[o] 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.
[p] Skin biopsies may also be performed on peripheral bullae intact skin. Two biopsies should be performed with one being sent for direct immunofluorescence testing in normal saline.
[q] The following serologic tests may be considered for autoimmune/irAE-associated bullous disorders: bullous pemphigoid antibodies, desmoglein 1,3 (pemphigus) antibodies, anti-skin antibody or indirect immunofluorescence.
[r] Asymptomatic; blisters covering <10% BSA.
[s] Blisters covering 10%–30% BSA; painful blisters; limiting iADLs.
[t] Blisters covering >30% BSA; limiting self-care ADLs.
[u] Blisters covering >30% BSA; associated with fluid or electrolyte abnormalities; intensive care unit (ICU) care or burn unit indicated.
[v] 1,000 mg once every 2 weeks for 2 doses (in combination with a tapering course of glucocorticoids), followed by maintenance of rituximab 500 mg at months 12 and 18 as needed. Joly P, Maho-Vaillant M, Prost-Squarcioni C, et al. First-line rituximab combined with short-term prednisone versus prednisone alone for the treatment of pemphigus (Ritux 3): a prospective, multicentre, parallel-group, open-label randomised trial. Lancet 2017;389:2031-2040.

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**GASTROINTESTINAL ADVERSE EVENT(S)**

- Diarrhea
- Colitis[a]

**ASSESSMENT/GRADING**

- Stool evaluation to rule out infectious etiology[b]
  - Nucleic acid amplification tests (NAATs) for GI pathogens/bacterial culture
  - *C. difficile*
  - Ova & parasites; molecular testing for *Giardia* and *Cryptosporidium* spp and *E. histolytica*; consider microsporidia, *Cyclospora/isospora* spp
  - Viral pathogens testing when available
  - Based on institutional availability, consider lactoferrin/calprotectin[c]
- Consider abdominal/pelvic CT with contrast if G2–G4 colitis[a]
- Consider GI consultation if G2–G4
  - Colonoscopy or flexible sigmoidoscopy ± esophagogastroduodenoscopy (EGD) with biopsy[c]

**MANAGEMENT[g]**

**Mild (G1)[d]**
- Consider holding immunotherapy[h]
- Loperamide or diphenoxylate/atropine for 2–3 days
  - If no improvement and not already done, obtain labs for infectious workup
- Hydration
- Close monitoring[i]
- If persistent or progressive symptoms, check lactoferrin
  - If positive, treat as G2 (below)
  - If negative and no infection, continue G1 management and add mesalamine, cholestyramine

**Moderate (G2)[e]**
- Hold immunotherapy[h]
- Prednisone/methylprednisolone[j] (1–2 mg/kg/day)[k]
- No response in 2–3 days, continue steroids, consider adding infliximab[l,m,n] or vedolizumab[n] within 2 weeks

**Severe (G3–4)[f]** → See ICI_GI-2

[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.

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| GRADING | MANAGEMENT[g] |
|---|---|
| Severe (G3–4)[f] diarrhea or colitis | • G3: Discontinue anti-CTLA-4; consider resuming anti-PD-1/PD-L1 after resolution of toxicity[h]<br>• G4: Permanently discontinue immunotherapy agent responsible for toxicity[h]<br>• Consider inpatient care for provision of supportive care<br>• Intravenous (IV) methylprednisolone[j] (1–2 mg/kg/day)[k]<br>▸ No response in 2 days, continue steroids, strongly consider adding infliximab[l,m,n] or vedolizumab[n] within 2 weeks[o] |

[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.

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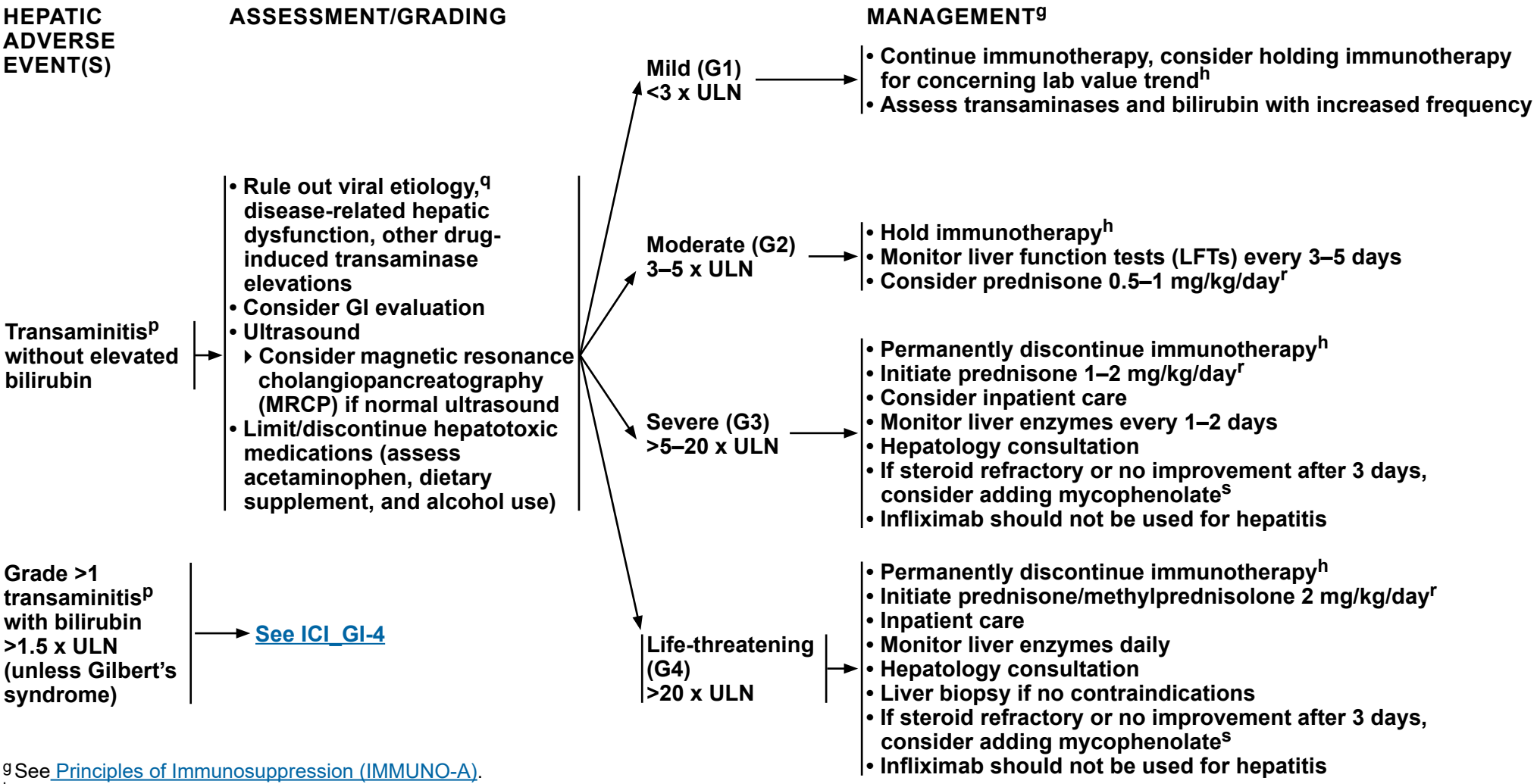


[g] See Principles of Immunosuppression (IMMUNO-A).
[h] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[p] Elevated alanine transaminase (ALT) and aspartate transaminase (AST).
[q] Consider initiating steroids while waiting for results in cases of life-threatening transaminitis.
[r] When liver 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.
[s] Mycophenolate mofetil treatment (0.5–1 g every 12 hours) can be considered in patients who have persistent severe hepatitis despite high-dose corticosteroids.

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| HEPATIC ADVERSE EVENT(S) | ASSESSMENT | MANAGEMENT[g] |
|---|---|---|
| Grade >1 transaminitis[p] with bilirubin >1.5 x ULN (unless Gilbert's syndrome) | • Rule out viral etiology, disease-related hepatic dysfunction, other drug-induced transaminase elevations<br>• Consider GI evaluation<br>• Limit/discontinue hepatotoxic medications (assess acetaminophen, dietary supplements, and alcohol use) | • Permanently discontinue immunotherapy[h]<br>• Initiate prednisone/methylprednisolone 2 mg/kg/day[r]<br>• Inpatient care<br>• Monitor liver enzymes daily<br>• Hepatology consultation<br>• If steroid refractory or no improvement after 3 days, consider adding mycophenolate[s]<br>• Infliximab should not be used for hepatitis |

[g] See Principles of Immunosuppression (IMMUNO-A).
[h] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[p] Elevated ALT and AST.
[r] 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.
[s] Mycophenolate mofetil treatment (0.5–1 g every 12 hours) can be considered in patients who have persistent severe hepatitis despite high-dose corticosteroids.

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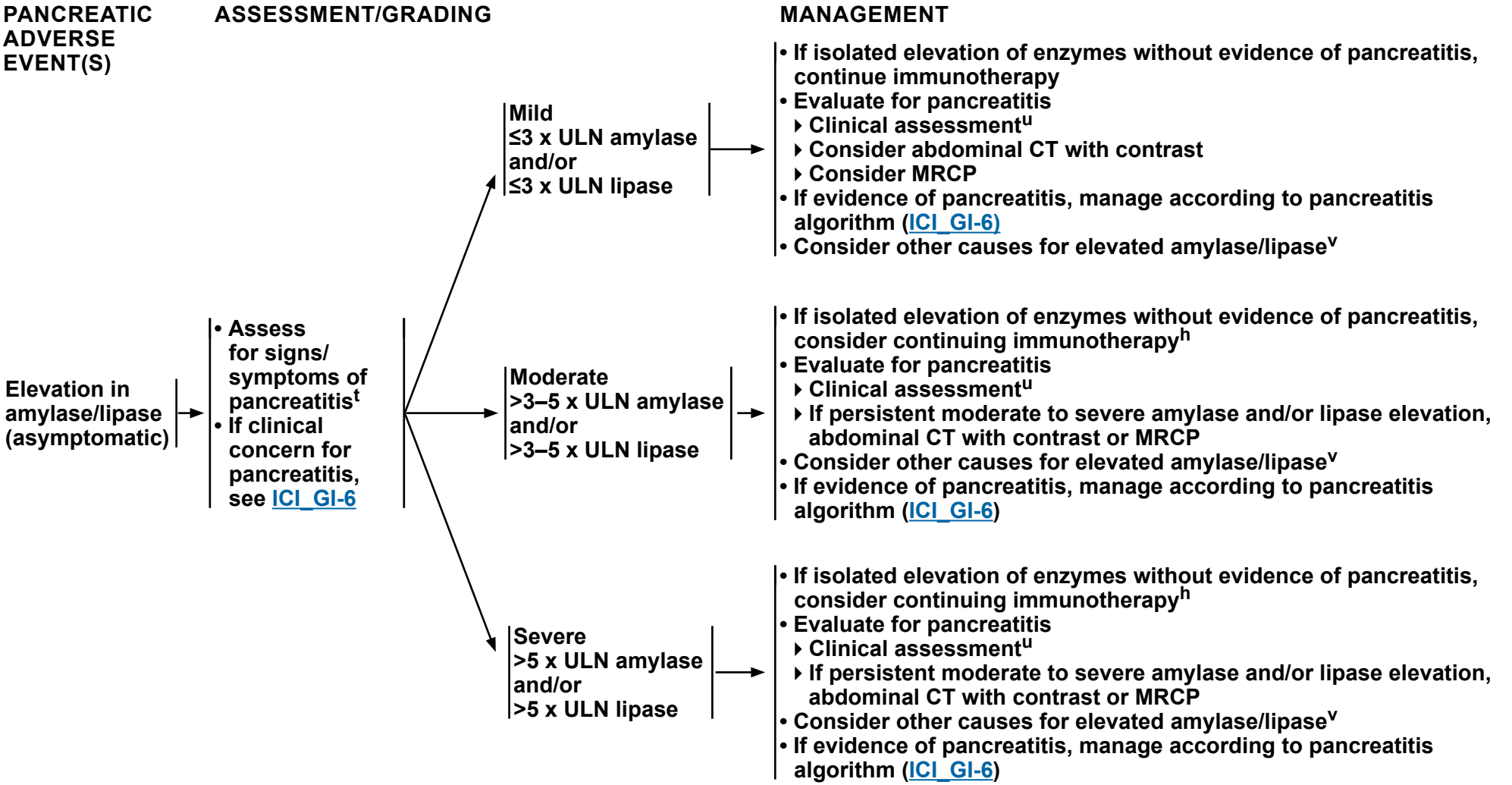


[h] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[t] Mild symptoms of pancreatitis can include: nausea, bloating, belching, abdominal pain, or back pain.
[u] Routine amylase/lipase assessments do not have to be performed outside of clinical suspicion of possible pancreatitis. See Principles of Routine Monitoring for Immune Checkpoint Inhibitors (IMMUNO-1).
[v] Inflammatory bowel disease, irritable bowel syndrome, bowel obstruction, gastroparesis, nausea/vomiting, medications, alcohol, and/or diabetes mellitus (DM).

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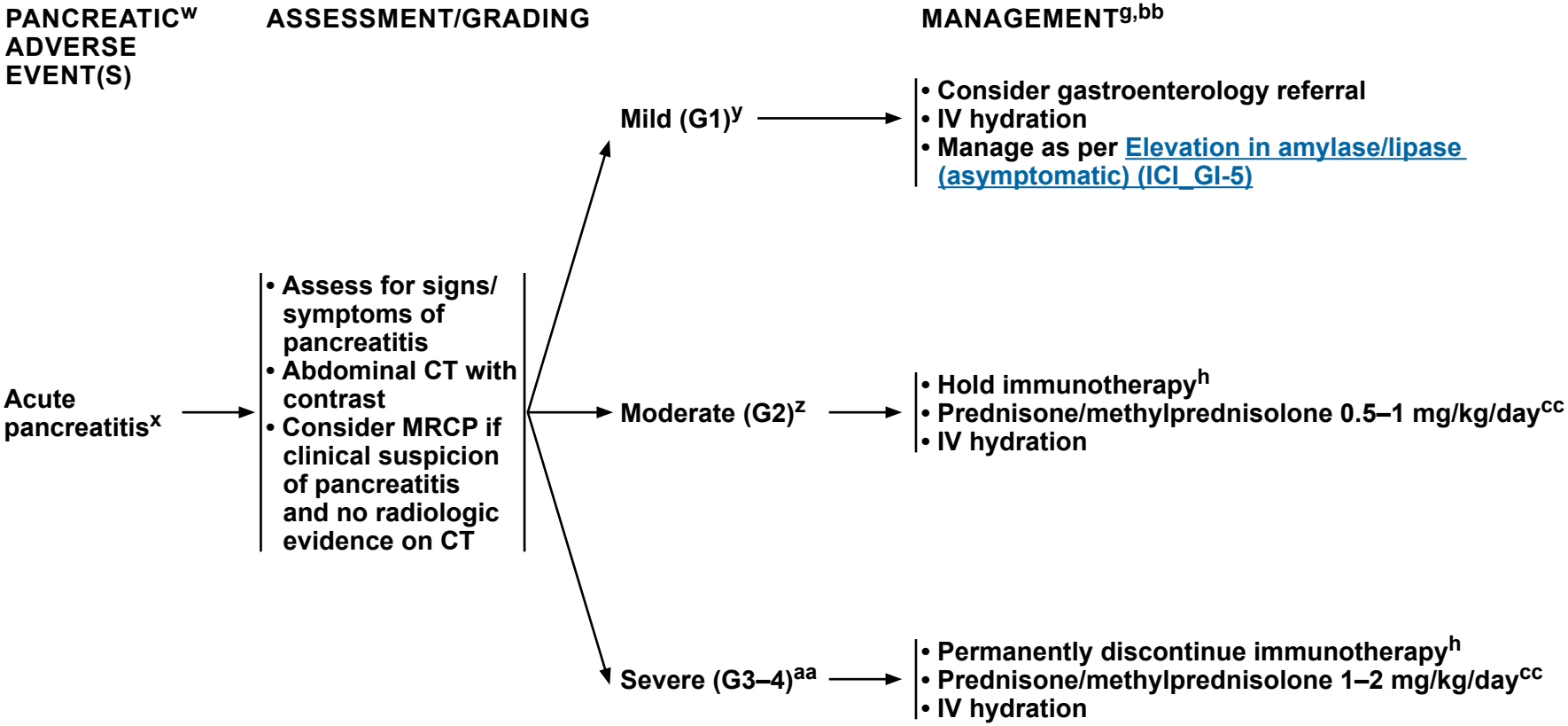


[g] See Principles of Immunosuppression (IMMUNO-A).
[h] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[w] No requirement for routine monitoring of potential pancreatitis with imaging.
[x] Provide standard medical care for signs and symptoms of acute pancreatitis, including hospital admission,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

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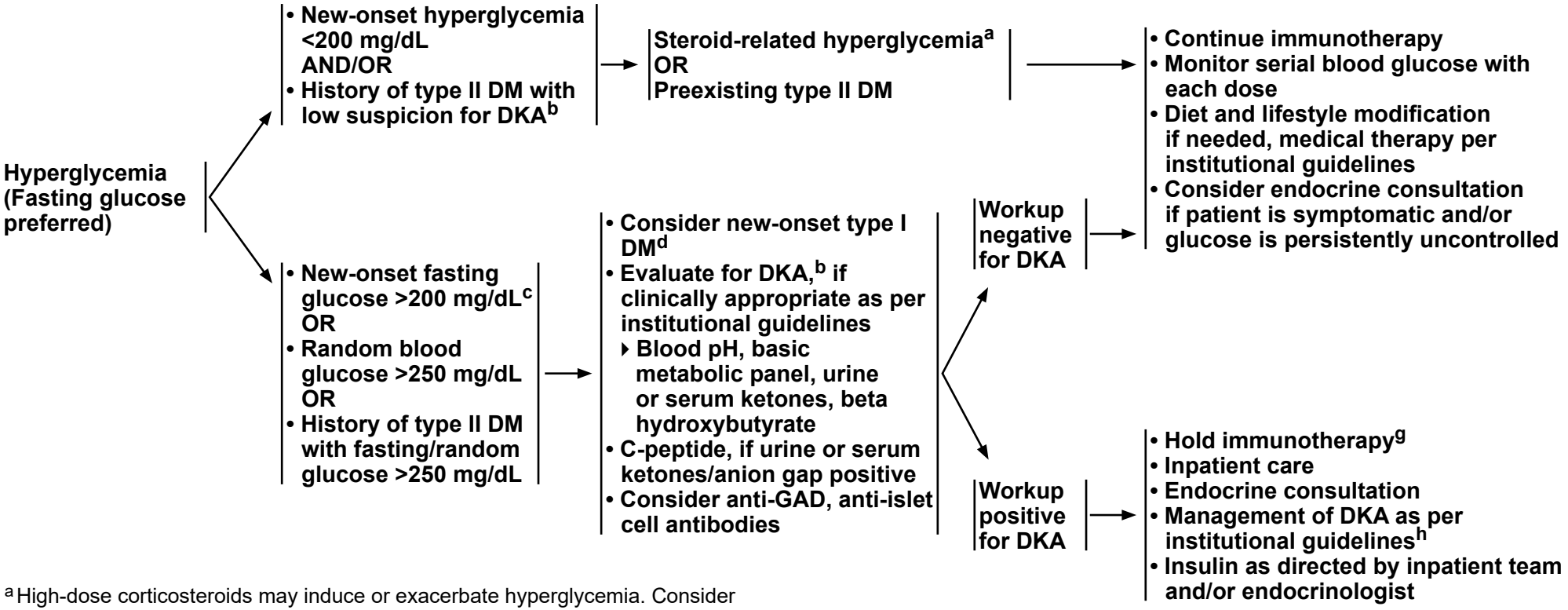


[a] High-dose corticosteroids may induce or exacerbate hyperglycemia. Consider endocrinology referral and appropriate management if symptomatic and/or persistently uncontrolled.

[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] In patients who are critically ill/ill-appearing with sugars >200 mg/dL (typically 300–500 mg/dL), urgent/emergent evaluation for DKA is indicated.

[d] The development of type I DM is rare 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.

[e] Evaluate for signs/symptoms of pancreatic exocrine insufficiency, and supplement if needed.

[f] Insufficient evidence to suggest corticosteroids may reverse type I DM induced by immunotherapy, and may complicate glycemic control.

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

[h] Institutional guidelines may include but are not limited to: IV fluids +/– potassium supplementation, IV insulin, hourly glucose, serum ketones, blood pH, and anion gap.

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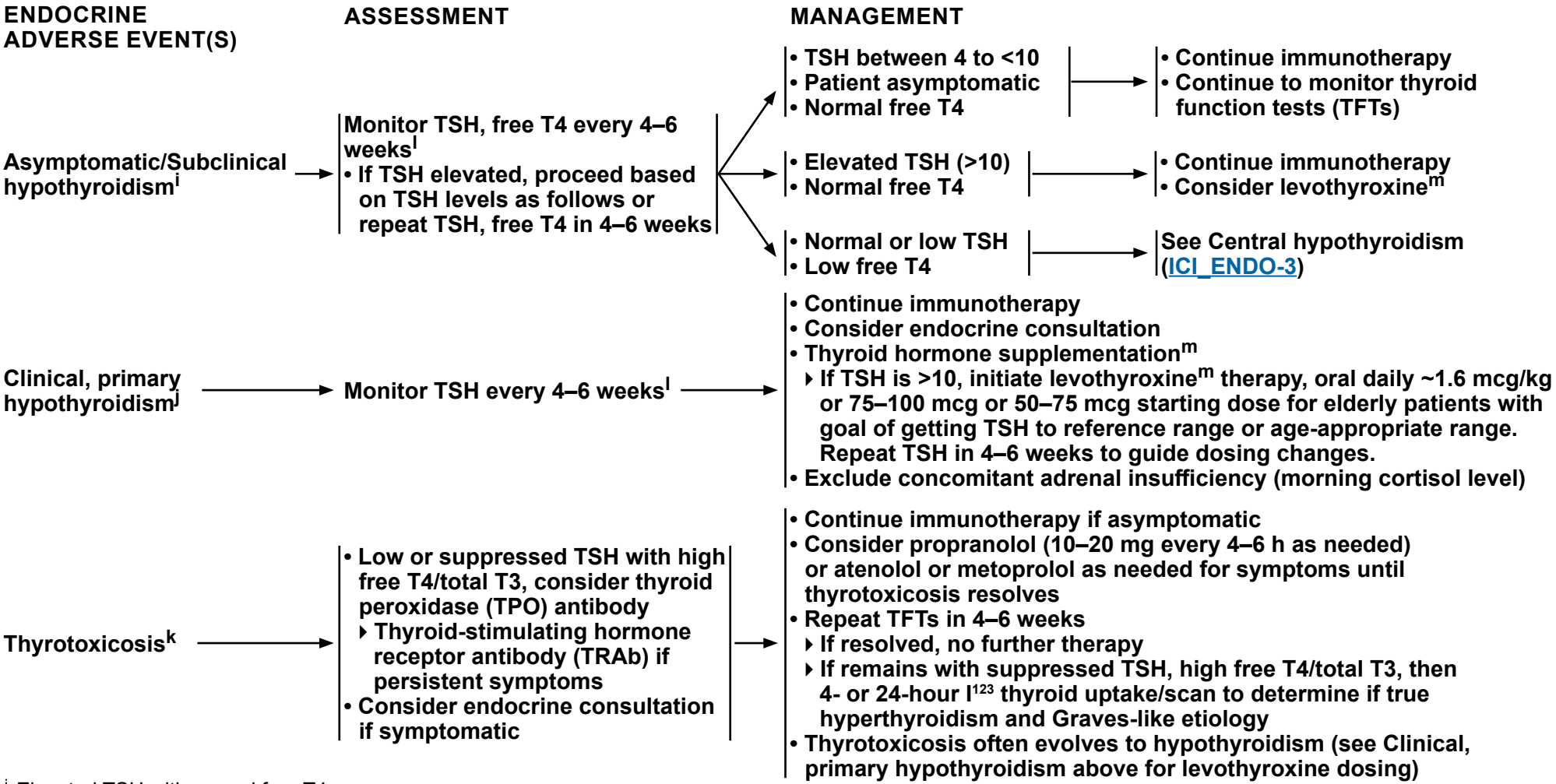


[i] Elevated TSH with normal free T4.
[j] Generally, elevated TSH (>10) with low free T4, clinical symptoms.
[k] Defined as suppressed TSH that may be: a) subclinical if free T4 normal, b) clinical if high free T4. The majority of suppressed TSH (<0.01) are due to transient or progressive painless thyroiditis.
[l] For patients without baseline thyroid function abnormalities or who are asymptomatic, can increase thyroid function testing interval to every 12–18 weeks as indicated.
[m] 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).

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| ENDOCRINE ADVERSE EVENT(S) | ASSESSMENT | MANAGEMENT[n] |
|---|---|---|
| Central hypothyroidism[p] | • Evaluate<br>▸ Morning cortisol and ACTH<br>▸ FSH, LH, TSH, free T4, DHEA-S<br>• Estradiol testing in women<br>• Testosterone testing in men<br>• Consider MRI of pituitary if confirmed central thyroid/adrenal insufficiency | • Consider holding immunotherapy until no longer symptomatic[g]<br>• Treat as hypophysitis (below)<br>• Follow free T4 for thyroid replacement in the setting of hypophysitis-induced loss of TSH production |
| Hypophysitis[q,r] | • Evaluate<br>▸ Morning cortisol and ACTH<br>▸ FSH, LH, TSH, free T4, testosterone in men, estrogen in premenopausal women<br>• MRI brain ± contrast with pituitary/sellar cuts, if symptomatic | • Consider endocrine consultation<br>• Hold immunotherapy until acute symptoms resolve[g,q]<br>• If symptomatic, prednisone/methylprednisolone 1–2 mg/kg/day[o]<br>• Hormone replacement as indicated[s]<br>• Follow free T4 for thyroid replacement in the setting of hypophysitis-induced loss of TSH production<br>• Patient education regarding stress doses of hydrocortisone for infection, trauma, etc.<br>▸ Alert bracelet is recommended |

[g] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[n] See Principles of Immunosuppression (IMMUNO-A).
[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] Low or suppressed TSH with inappropriately low free T4 may represent sequela of hypophysitis; for which other pituitary axes may be affected.
[q] 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 morning cortisol, low Na, low K, and low testosterone. Non-acute symptoms may include fatigue and possible weight loss.
[r] If a patient has polyuria/polydipsia, consider workup for diabetes insipidus; however, this is exceedingly rare with only a few case reports.
[s] 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, testosterone supplementation in males, and estrogen in pre-menopausal women if not otherwise contraindicated. Patients may require physiologic replacement hormones indefinitely.

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| ENDOCRINE ADVERSE EVENT(S) | ASSESSMENT/GRADING | MANAGEMENT[n,o] |
|---|---|---|
| Primary adrenal insufficiency[t] | • Evaluate morning cortisol and ACTH levels<br>• Comprehensive metabolic panel (Na, K, $CO_2$, glucose)[u] | • Hold immunotherapy[g]<br>• Endocrine consultation<br>▸ Endocrine evaluation prior to surgery or any procedure<br>• *Start corticosteroid first before other hormone replacement to avoid adrenal crisis*<br>• Steroid replacement[v,w] and monitor electrolytes<br>▸ Hydrocortisone 20 mg in AM, 10 mg in PM, then slowly titrating doses down according to symptoms[x]<br>OR<br>▸ Prednisone 7.5 mg or 10 mg starting dose, then reduce to 5 mg daily as appropriate<br>AND<br>Fludrocortisone can be started 0.1 mg daily or every other day; then titrated up or down based on blood pressure, symptoms, lower-extremity edema, and labs<br>• If hemodynamically unstable, inpatient care and initiate high-dose/stress-dose steroids<br>• Patients with severe symptoms (hypotension) may require additional fluids (eg, normal saline often >2 L required)<br>• Patient education regarding stress doses of hydrocortisone for infection, trauma, etc.<br>▸ Alert bracelet is recommended |

[g] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[n] See Principles of Immunosuppression (IMMUNO-A).
[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.
[t] 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.
[u] To rule out central hypothyroidism.
[v] If acutely ill, double or triple these doses for 24–48 hours (ie, sick day rules for fever >101, nausea/emesis, surgeries).
[w] Will require physiologic replacement steroids indefinitely.
[x] 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.

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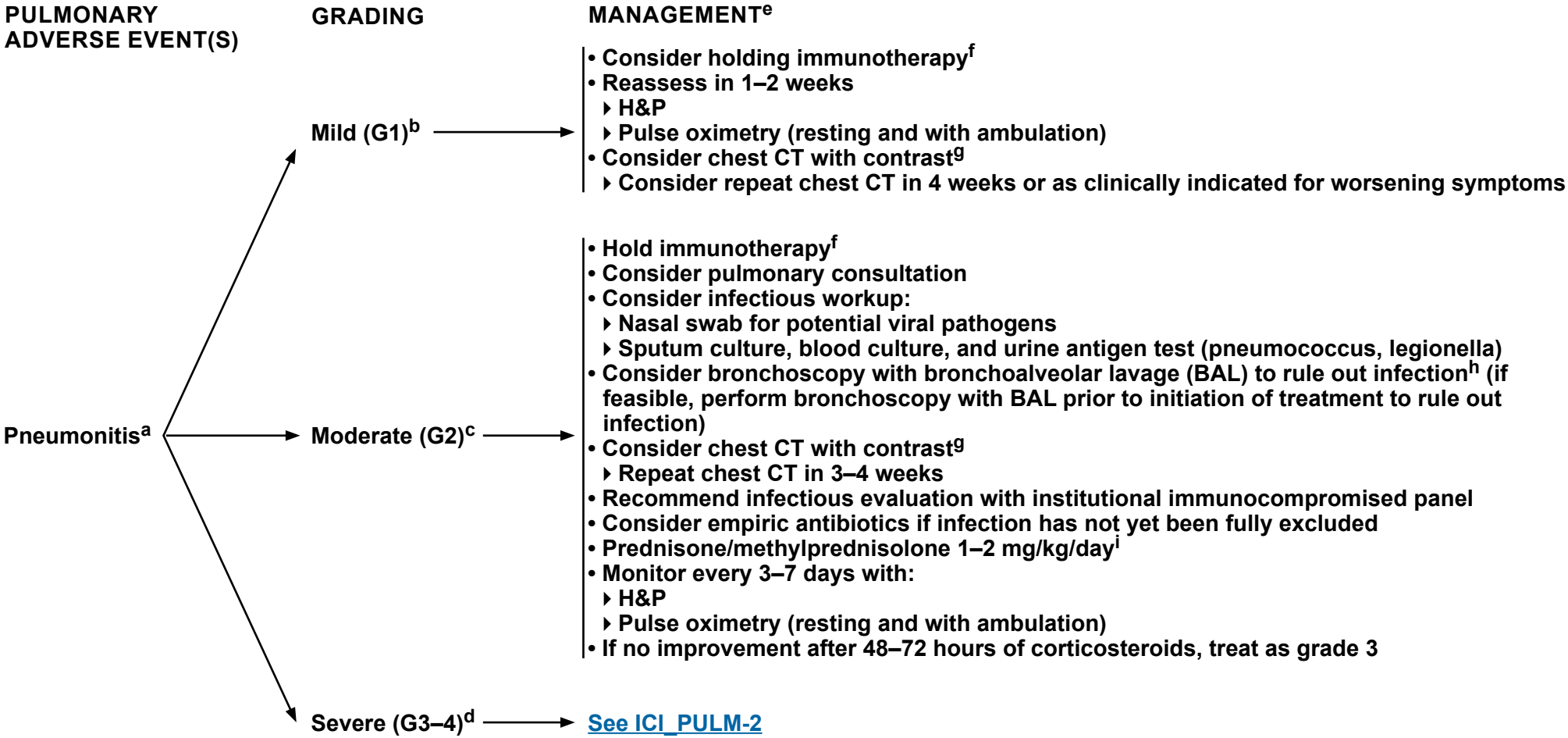


[a] Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging as ground-glass opacities) with or without dry cough. Consider infectious etiologies.
[b] Asymptomatic; confined to one lobe of the lung or <25% of lung parenchyma; clinical or diagnostic observations only.
[c] 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, oxygen indicated; G4–life-threatening respiratory compromise.
[e] See Principles of Immunosuppression (IMMUNO-A).
[f] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[g] CT with contrast to rule out other etiologies if not contraindicated.
[h] If concern for lymphangitic spread of tumor, biopsy is indicated.
[i] Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.

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| ASSESSMENT/ GRADING | MANAGEMENT[e] |
|---|---|
| Severe (G3–4)[d] pneumonitis[a] | • Permanently discontinue immunotherapy[f]<br>• Inpatient care<br>• Infectious workup:<br>▸ Consider that patient may be immunocompromised<br>▸ Nasal swab for potential viral pathogens<br>▸ Sputum culture, blood culture, and urine culture<br>• Pulmonary and infectious disease consultation<br>• Bronchoscopy with BAL to rule out infection and malignant lung infiltration<br>• Consider empiric antibiotics if infection has not yet been fully excluded<br>• Methylprednisolone 1–2 mg/kg/day. Assess response within 48 hours and plan taper over ≥6 weeks<br>• Consider adding any of the following if no improvement after 48 hours:[j]<br>▸ Infliximab[k] 5 mg/kg IV, a second dose may be repeated 14 days later at the discretion of the treating provider<br>▸ Intravenous immunoglobulin (IVIG)[l]<br>▸ Mycophenolate mofetil 1–1.5g BID then taper in consultation with pulmonary service |

[a] Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging as ground-glass opacities) with or without dry cough. Consider infectious etiologies.
[d] G3-severe symptoms involve all lung lobes or >50% of lung parenchyma; limiting self-care ADLs, oxygen indicated; G4–life-threatening respiratory compromise.
[e] See Principles of Immunosuppression (IMMUNO-A).
[f] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[j] Options are listed in alphabetical order. There are no data to support the use of one over another.
[k] An FDA-approved biosimilar is an appropriate substitute for infliximab.
[l] Total dosing should be 2 g/kg, administered in divided doses over 2 to 5 days as per package insert.

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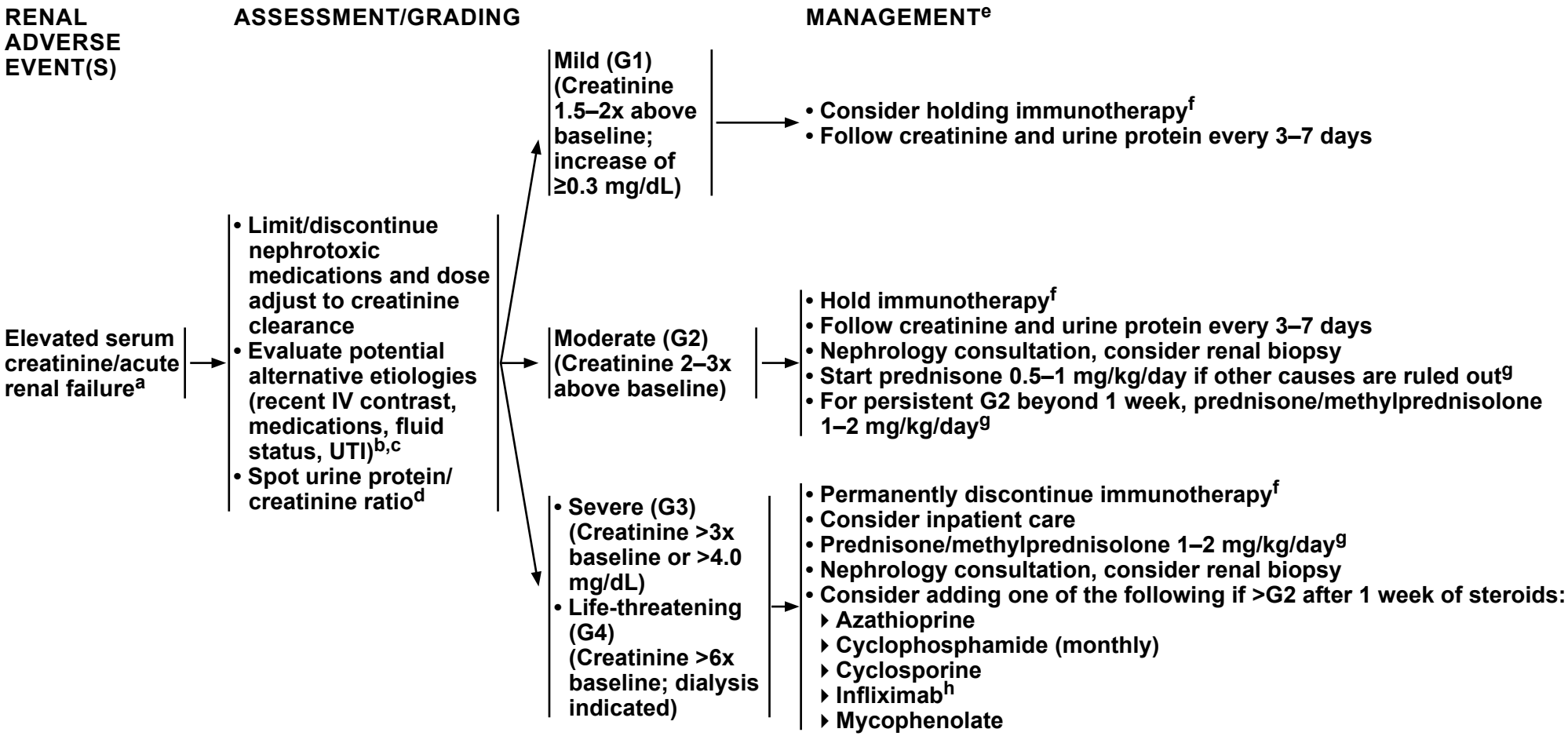


[a] Azotemia, creatinine elevation, inability to maintain acid/base or electrolyte balance, and urine output change.

[b] General medical review and testing as warranted for prerenal and postrenal causes. Include medication review for nephrotoxic agents such as NSAIDs and PPIs, and consider obstruction, cardiomyopathy/heart failure, pulmonary hypertension, diuretics, hypovolemia due to primary GI cause, stones, and infection.

[c] Distinguish cell infiltrate (consider vasculitis) 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).

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

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

[h] An FDA-approved biosimilar is an appropriate substitute for infliximab.

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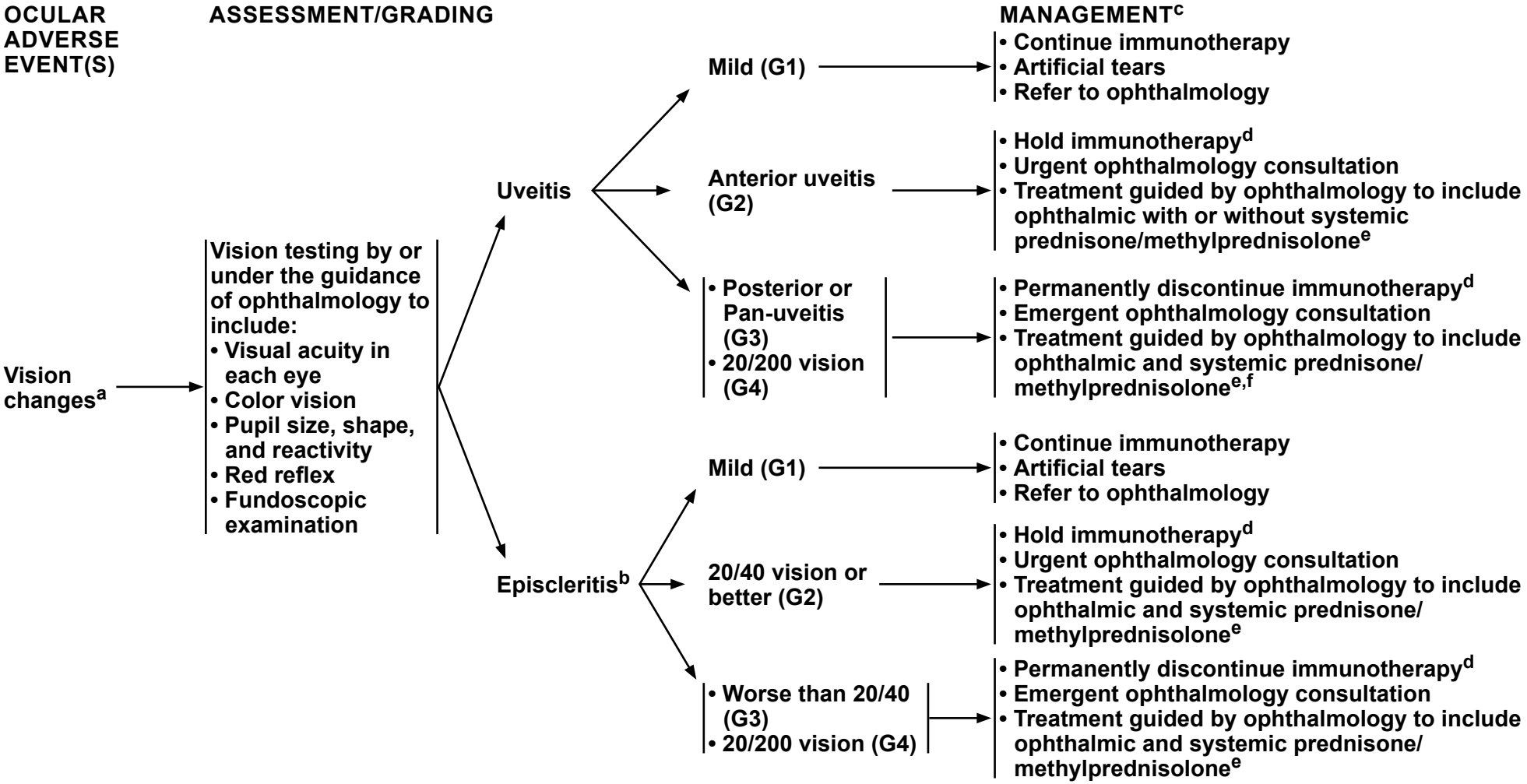


[a] Patients experiencing ocular adverse events (AEs) may present with any of the following symptoms: blurred/distorted vision, blind spots, change in color vision, photophobia, tenderness/pain, eyelid swelling, and proptosis. Episcleritis can be associated with red or purple discoloration of the eye.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

[b] Treat blepharitis per the episcleritis algorithm.

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

[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, FDA-approved biosimilar, or antimetabolites (eg, methotrexate) for pan-uveitis.

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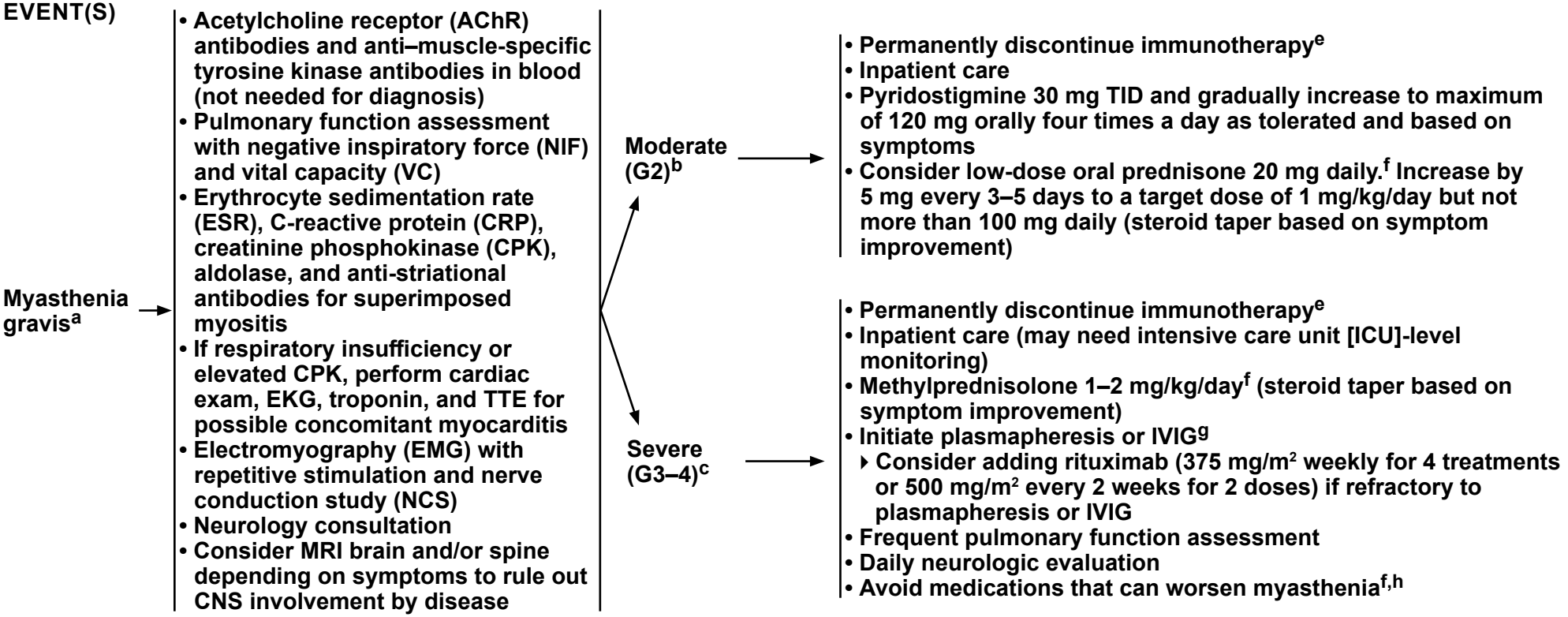


[a] Progressive or fluctuating muscle weakness, generally proximal to distal. May have bulbar involvement (ie, ptosis, extraocular movement abnormalities resulting in double vision, dysphagia, facial muscle weakness) and/or respiratory muscle weakness. May occur with myositis and myocarditis. Respiratory 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).

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

[f] High-dose steroids (≥2 mg/kg/day) may exacerbate symptoms.

[g] Total dosing should be 2 g/kg, administered in divided doses per package insert.

[h] Beta-blockers, ciprofloxacin, and IV magnesium.

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| NERVOUS SYSTEM ADVERSE EVENT(S) | ASSESSMENT/GRADING | | MANAGEMENT[d] |
|---|---|---|---|
| Guillain-Barré syndrome (GBS)[i] | • Inpatient care with access to ICU-level monitoring<br>• Neurology consultation<br>• MRI of spine with or without contrast (rule out compressive lesion)<br>• Lumbar puncture[j]<br>• Serum ganglioside antibody tests for GBS variants (GQ1b for Miller Fisher variant associated with ataxia and ophthalmoplegia)<br>• Pulmonary function testing (NIF/VC) | Moderate (G2)[k]<br>or<br>Severe (G3–4)[l] | • Permanently discontinue immunotherapy[e]<br>• Inpatient care with capability of rapid transfer to ICU-level monitoring<br>• Start IVIG[g] or plasmapheresis in addition to pulse-dose methylprednisolone 1 gram daily for 5 days[m] then taper over 4 weeks<br>• Frequent neurologic evaluation and pulmonary function monitoring<br>• Monitor for concurrent autonomic dysfunction<br>• Gabapentin, pregabalin, or duloxetine for pain |

[d] See Principles of Immunosuppression (IMMUNO-A).
[e] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[g] Total dosing should be 2 g/kg, administered in divided doses per package insert.
[i] Progressive, most often symmetrical muscle weakness with absent or reduced deep tendon reflexes. May involve extremities, facial, respiratory, and bulbar and oculomotor nerves. May have dysregulation of autonomic nerves. Often starts with pain in lower back and thighs.
[j] 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.
[k] Some interference with ADLs, symptoms concerning to patient.
[l] Limiting self-care and aids warranted, weakness limiting walking, any dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms.
[m] Steroids are not usually recommended for idiopathic GBS; however, in immunotherapy-related forms, a trial is reasonable in addition to IVIG or plasmapheresis.

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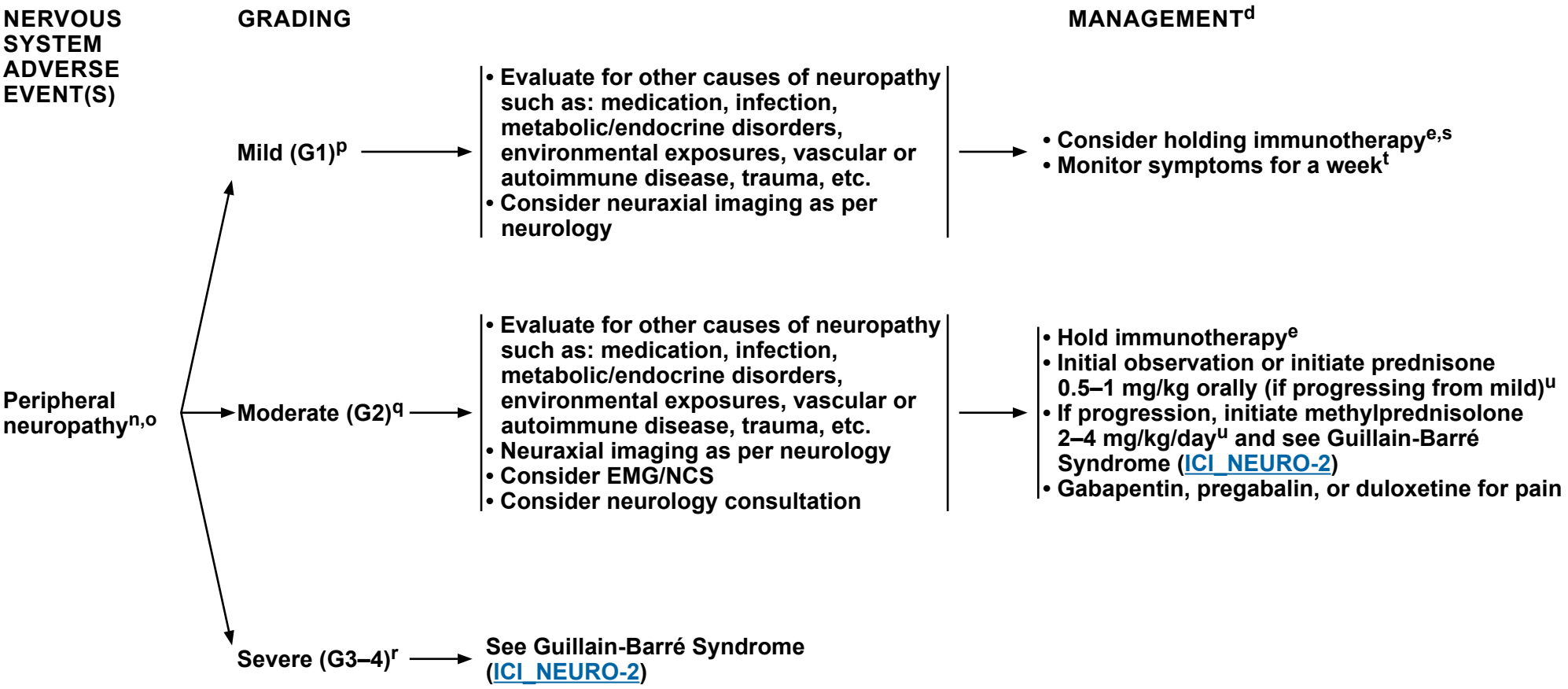


[d] See Principles of Immunosuppression (IMMUNO-A).
[e] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[n] Can present as asymmetric or symmetric sensory-motor deficit. Sensory deficit may be painful or painless parasthesias or potentially life-threatening autonomic (eg, myenteric plexus) dysfunction. Hypo- or areflexia. Isolated sensory deficit or sensory plus lower motor neuron deficit.
[o] 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.
[p] No interference with function and symptoms not concerning to patient. Note: any cranial nerve problem should be managed as moderate.
[q] Some interference with ADLs, symptoms concerning to patient (ie, pain but no weakness or gait limitation).
[r] 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.
[s] There is a low threshold to hold immune checkpoint inhibitors in mild cases of peripheral neuropathy.
[t] Specifically monitor for new interference with iADLs from either pain or weakness, gait difficulty, ataxia, or autonomic changes.
[u] Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.

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| NERVOUS SYSTEM ADVERSE EVENT(S) | ASSESSMENT | MANAGEMENT[d] |
|---|---|---|
| **Aseptic meningitis[v,w]** | • MRI brain with and without contrast + pituitary protocol<br>• Morning cortisol, to rule out adrenal insufficiency<br>• Consider lumbar puncture[y] if feasible<br>• Consider neurology consultation | • Hold immunotherapy[e] if mild/moderate<br>• Permanently discontinue immunotherapy if severe<br>• Inpatient care (G3–4[bb])<br>• Consider IV acyclovir[dd] until polymerase chain reaction (PCR) results obtained<br>• Rule out bacterial and viral infection, then may closely monitor off steroids or consider prednisone 0.5–1 mg/kg/day or methylprednisolone 1–2 mg/kg/day if moderate/severe symptoms[cc] |
| **Encephalitis[w,x]** | • Neurology consultation<br>• MRI brain with and without contrast[z]<br>• Lumbar puncture[aa]<br>• EEG to evaluate for subclinical seizures<br>• Comprehensive metabolic panel, CBC, ESR, CRP, antineutrophil cytoplasmic antibody (ANCA) (if vasculitic process suspected), thyroid panel including TPO and thyroglobulin<br>• Autoimmune encephalopathy and paraneoplastic panel in CSF and serum | • Hold immunotherapy[e] if mild<br>• Permanently discontinue immunotherapy if moderate/severe<br>• Inpatient care (G3–4[bb])<br>• Consider IV acyclovir[dd] until PCR results obtained<br>• Trial of methylprednisolone 1–2 mg/kg/day[cc]<br>• If severe or progressing symptoms or oligoclonal bands present, consider pulse steroids methylprednisolone 1 g IV daily for 3–5 days plus IVIG[g] or plasmapheresis<br>• If positive for autoimmune encephalopathy antibody or limited or no improvement after 7–14 days, consider rituximab |

[d] See Principles of Immunosuppression (IMMUNO-A).
[e] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[g] Total dosing should be 2 g/kg, administered in divided doses per package insert.
[v] 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).
[w] Exclude infectious causes, especially viral (ie, HSV).
[x] Confusion, altered behavior, headaches, seizures, short-term memory loss, depressed level of consciousness, focal weakness, and speech abnormality.
[y] 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, gram stain, and elevated protein. May see reactive lymphocytes or histiocytes on cytology.
[z] May reveal T2/FLAIR changes typical of what is seen in autoimmune encephalopathies or limbic encephalitis or may be normal.
[aa] 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.
[bb] Limiting self-care and aids warranted.
[cc] Taper steroids over 4 weeks once symptoms resolve.
[dd] 10 mg/kg IV every 8 hours.

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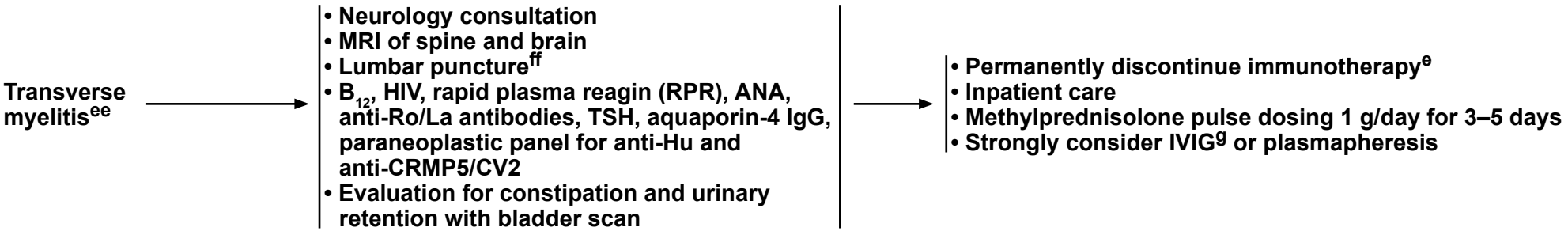


[d] See Principles of Immunosuppression (IMMUNO-A).
[e] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[g] Total dosing should be 2 g/kg, administered in divided doses per package insert.
[ee] Acute or subacute weakness or sensory changes bilaterally, often with increased deep tendon reflexes.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

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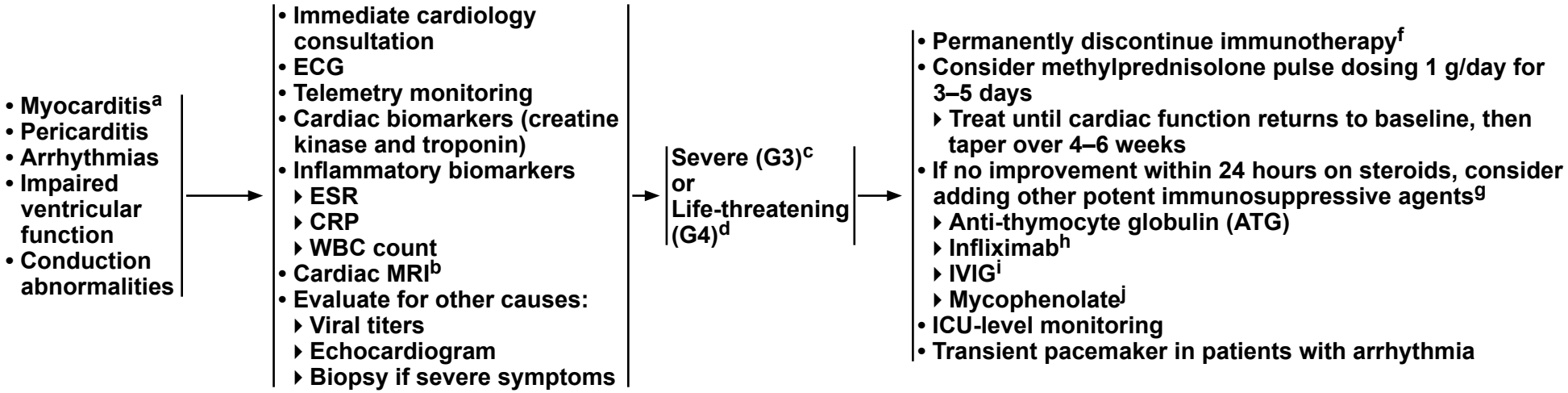


[a] Myocarditis symptoms are nonspecific. It is rare, but potentially severe, not viral in etiology, associated with myositis/myasthenia gravis, and is more common with combination therapy. In fatal cases, conduction abnormalities were mode of death and ejection fraction was preserved.
[b] No evidence 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).

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**MUSCULOSKELETAL ADVERSE EVENT(S)**

**ASSESSMENT/GRADING**

**Inflammatory arthritis[a]**

- Number of joints involved
- Functional assessment
- X-ray, joint ultrasound, or joint MRI

**MANAGEMENT[d]**

**Mild[b]**

- Continue immunotherapy
- NSAIDs
  - If NSAIDs ineffective, consider low-dose prednisone 10–20 mg daily x 4 weeks; if not improving, treat as moderate
- Consider intra-articular steroids in affected joint(s), depending on joint location and number involved

**Moderate**

- Consider holding immunotherapy[e]
- Prednisone 0.5 mg/kg/day x 4–6 weeks,[f] treat as severe if no improvement
- If no improvement by week 4 strongly recommend rheumatology consultation

**Severe[c]**

- Hold or permanently discontinue[e,g] immunotherapy
- Prednisone/methylprednisolone 1 mg/kg/day[f]
  - If no improvement by week 2, rheumatology consultation for consideration of additional disease modifying anti-rheumatic drugs depending on clinical phenotype of inflammatory arthritis. Options include: infliximab,[h] methotrexate, tocilizumab, sulfasalazine, azathioprine, leflunomide, IVIG[i]

**Monitor with serial rheumatologic examinations ± ESR, CRP every 4–6 weeks after treatment[j]**

[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).
[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] An FDA-approved biosimilar is an appropriate substitute for infliximab.
[i] Consider co-existence of other irAEs in which choice of immunosuppression may be relevant.
[j] Consider ESR, CRP to monitor response if elevated at the onset of therapy.

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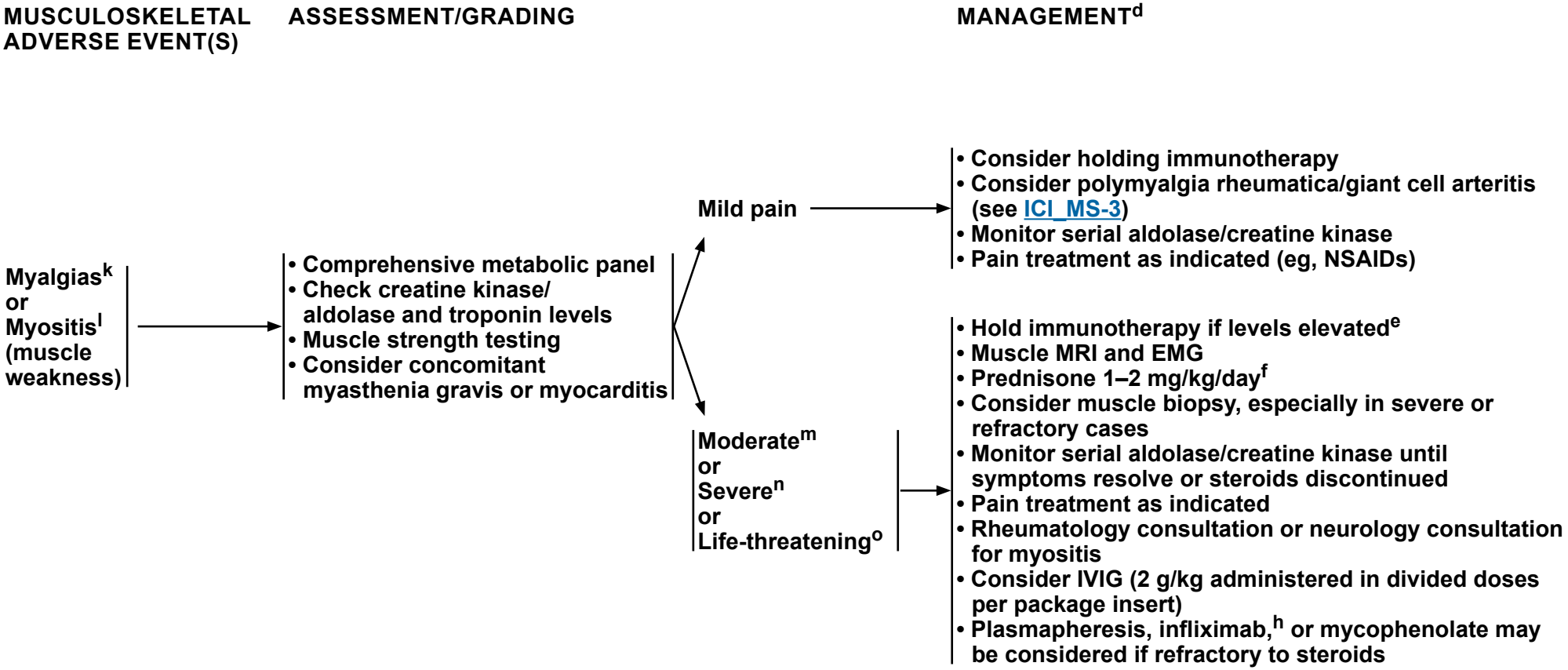


[d] See Principles of Immunosuppression (IMMUNO-A).
[e] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[f] Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[h] An FDA-approved biosimilar is an appropriate substitute for infliximab.
[k] Myalgia is a disorder characterized by marked discomfort sensation originating from a muscle or group of muscles.
[l] Myositis is a disorder characterized by inflammation and/or weakness involving the skeletal muscles.
[m] Moderate pain associated with weakness or elevated CK or aldolase; limiting self-care ADLs.
[n] For myalgias, moderate pain associated with weakness; pain limiting iADLs. In myositis, pain associated with severe weakness; limiting self-care ADLs.
[o] Only applies to myositis; urgent intervention indicated.

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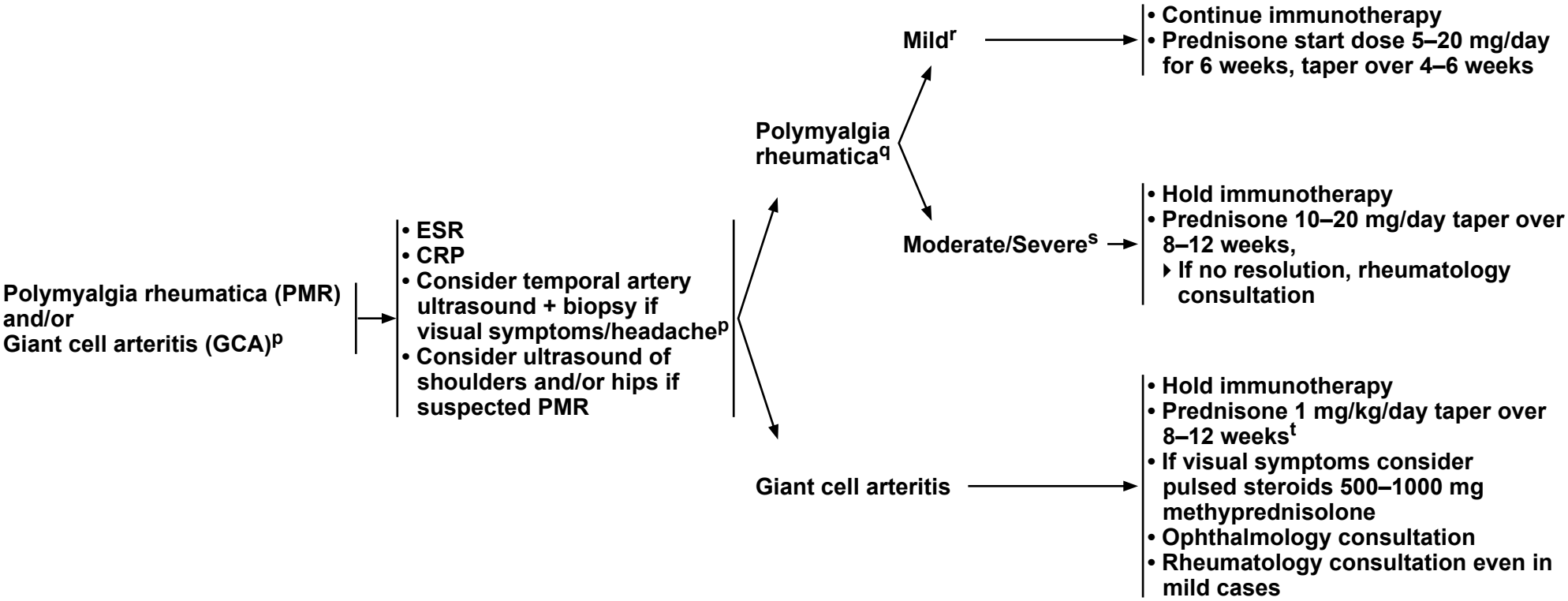
**MUSCULOSKELETAL ADVERSE EVENT(S)**

**ASSESSMENT/GRADING**

**MANAGEMENT[d]**




[d] See Principles of Immunosuppression (IMMUNO-A).
[p] GCA symptoms: visual symptoms, headache, scalp tenderness, jaw claudication.
[q] Calabrese C, Kirchner E, Kontzias K, et al. Rheumatic immune-related adverse events of checkpoint therapy for cancer: case series of a new nosological entity. RMD Open 2017;3:e000412; Calabrese C, Cappelli LC, Kostine M, et al. Polymyalgia rheumatica-like syndrome from checkpoint inhibitor therapy: case series and systematic review of the literature. RMD Open 2019;5:e000906.
[r] Mild symptoms of pain and/or stiffness, not limiting ADLs.
[s] Pain and/or stiffness that limits instrumental or self-care activities of daily living.
[t] Patients with giant cell arteritis require a slower taper. Goldstein BL, Gedmintas L, Todd DJ. Drug-associated polymyalgia rheumatica/giant cell arteritis occurring in two patients after treatment with ipilimumab, an antagonist of CTLA-4. Arthritis Rheumatol 2014;66:768-769; Micaily I, Chernoff M. An Unknown Reaction to Pembrolizumab: Giant Cell Arteritis. Ann Oncol. 2017;28:2621-2622, Calabrese LH, Calabrese C, Cappelli LC. Rheumatic immune-related adverse events from cancer immunotherapy. Nat Rev Rheumatol 2018;14:569-579.

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## PRINCIPLES OF IMMUNOSUPPRESSION FOR PATIENTS RECEIVING IMMUNE CHECKPOINT INHIBITOR IMMUNOTHERAPY

### General Principles

- Close consultation with disease-specific subspecialties is encouraged.
  - Referral to a tertiary care center may be required for management of complex cases or multi-system immune-related adverse events (irAEs).
- Selected irAEs including hypothyroidism and other endocrine irAEs may be treated with hormonal supplementation, without the need for corticosteroid therapy. See Endocrine Toxicities section.
- Vaccines that are inactivated or killed preparations are permissible during a course of immunotherapy. Due to the lack of clarity regarding live vaccine use, it is not recommended during ICI therapy.

### Principles of Steroid Use in the Management of irAEs

- Corticosteroids are the mainstay of treatment of most irAEs related to immunotherapy.
- Early intervention with corticosteroids is a key goal in general management of immune-related toxicity.
- Use of corticosteroids to treat irAEs has NOT been shown to reduce anti-tumor efficacy.
  - In the absence of specific indications such as prior infusion reaction or concurrent chemotherapy, routine premedication with corticosteroids is not recommended given the potential mitigation of immunotherapeutic effectiveness in the prophylactic setting.
- Steroid Dosing
  - See individual toxicity pages for specific recommendations on steroid dose by grade. Where immunotherapy rechallenge is indicated, see the Principles of Immunotherapy Rechallenge (IMMUNO-C) for guidance by organ site.
  - For neurologic, cardiac, or grade 3 or 4 irAEs, higher dose steroids (eg, methylprednisolone or prednisone 1–2 mg/kg/day) should be given.
  - Higher potency (eg, Class 2 or 3) topical corticosteroids are preferred for short-term use for immune-related dermatitis, compared to longer term use of lower potency steroids.
- Steroid Taper
  - Longer steroid tapers (>4 weeks, sometimes 6–8 weeks or longer) may be required to prevent recurrent irAE events, particularly pneumonitis and hepatitis.
- Prophylaxis
  - Prophylaxis against pneumocystis jiroveci pneumonia (PJP) can be considered in patients receiving a prednisone equivalent of 20 mg or more daily for 4 or more weeks. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.
  - Prophylaxis against fungal infections (eg, fluconazole) can be considered in patients receiving a prednisone equivalent of 20 mg or more daily for 6–8 or more weeks.
  - Prophylaxis against herpes zoster reactivation can be considered. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.
  - Proton pump inhibitor (PPI) therapy or H2 blockers can be considered for patients at higher risk of gastritis (eg, NSAID use, anticoagulation) for the duration of corticosteroid therapy.
  - If patients need to be on long-term steroids, they are at risk for developing osteoporosis. Vitamin D and calcium supplementation should be provided to prevent osteoporosis. Referral to physical therapy and weight-bearing exercises are recommended.

Continued

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### PRINCIPLES OF IMMUNOSUPPRESSION FOR PATIENTS RECEIVING IMMUNE CHECKPOINT INHIBITOR IMMUNOTHERAPY

**Principles of Anti-TNFα Agents and Other Immunosuppressants**

- **Anti-TNFα agents (eg, infliximab or FDA-approved biosimilar) are particularly effective in management of immune-related colitis and inflammatory arthritis.**

**Viral Reactivation**

- **There is a risk for hepatitis B virus reactivation with infliximab. Test for viral hepatitis B and hepatitis C prior to TNF inhibition and monitor HBV/HCV carriers during and for several months after therapy.**
- **There is a risk for tuberculosis (TB) activation. Test for latent/active TB prior to TNF inhibition. TB testing should not delay initiation of anti-TNFα agents for the management of irAEs.**
  - **Results of TB testing need not be finalized prior to dosing anti-TNFα agents in the acute setting.**
  - **Interferon-gamma release assays for TB testing are preferred.**

**Indications for anti-TNFα Therapy**

- **For patients with severe irAEs not responsive to steroids within 48–72 hours, early (~72 h) initiation of anti-TNFα therapy (eg, infliximab 5 mg/kg) may be warranted in consultation with the relevant medical specialist.**
  - **Close monitoring and follow-up of patients on steroids and infliximab is required to assess for response.**
  - **Additional doses of anti-TNFα therapy may be required, and should be administered 2 and 6 weeks after initial dose of infliximab or FDA-approved biosimilar.**
- **Anti-TNFα agents should be avoided in patients with immune-related hepatitis.**
  - **Alpha-4 beta-7 integrin inhibitors (eg, vedolizumab) may be considered in these cases for management of immune-related colitis and concomitant hepatitis (where infliximab is contraindicated).**
  - **Other immunosuppressive agents may be of use in certain irAEs; see individual toxicity pages.**

Continued

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### PRINCIPLES OF IMMUNOSUPPRESSION FOR PATIENTS RECEIVING IMMUNE CHECKPOINT INHIBITOR IMMUNOTHERAPY

**Principles of Immune Checkpoint Blockade in Patients with Pre-Existing Autoimmune Conditions or Organ Transplant Recipients**

- Patients with a history of HIV or viral hepatitis may be candidates for immunotherapy.
- Patients with pre-existing autoimmune conditions or organ transplant recipients may be candidates for immune checkpoint blockade.
- Patients with autoimmune neurologic conditions or life-threatening autoimmune disorders, particularly if not controlled with immunosuppressive medications or requiring high doses of immunosuppression, are unlikely to be suitable candidates for cancer immunotherapy.
- Patients with prior allogeneic stem cell transplant may be candidates for immunotherapy.

**Considerations for Patients with Pre-existing Autoimmune Conditions**

- Anti–CTLA-4-based therapy has a higher incidence of exacerbating baseline autoimmune conditions relative to anti-PD-1/PD-L1–based approaches.
- Optimization of immunosuppression for pre-existing autoimmune conditions, including close follow-up with pertinent subspecialists, is recommended.
  - Goal of immunosuppressive regimen allowing for dose of prednisone <10 mg daily or equivalent prior to initiating cancer immunotherapy.

**Considerations for Organ Transplant Recipients**

- Graft failure while on cancer immunotherapy has been reported. Transplant organ loss may be an outcome of treatment with cancer immunotherapy and should be discussed with patient and organ transplant team.
  - Patients with solid organ transplantation who have a viable option for alternative therapy if there is graft rejection (eg, kidney) may be candidates for immunotherapy, particularly if there is no prior evidence of graft rejection and if the patient is on maintenance immunosuppression.

**Consideration for Patients with Prior Allogeneic Stem Cell Transplant**

- There is an increased risk of transplant-related complications, including potentially fatal graft-versus-host disease (GVHD).
- Careful discussion with patient and stem cell transplant physicians should precede initiation of immunotherapy.

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### PRINCIPLES OF IMMUNOTHERAPY PATIENT EDUCATION

### HEALTH CARE PROVIDER (HCP) INFORMATION

**Prior to Starting Immune Checkpoint Inhibitor (ICI) Therapy:**

- Assess patient's understanding of disease and recommendations for treatment.
- Educate patients about mechanism of action and rationale for use of immune checkpoint inhibitors.
- Document any underlying medical conditions affecting any organ system (eg, pulmonary, cardiac, neurologic, musculoskeletal).
- It is important to take a history of any autoimmune diseases.
- Record all medications, including over-the-counter medications and herbal supplements.
- Patients of reproductive age should be advised to use effective birth control during and for at least 5 months after the final dose of immunotherapy.
  - The effect of immunotherapy on human reproductive function is unknown. Consider fertility preservation and reproductive endocrinology referral for all patients starting therapy who have not yet completed family planning.
- Breastfeeding is contraindicated during and for at least 5 months after the final dose of immunotherapy.
- Provide patients with and instruct them to carry a wallet card that outlines the type of immunotherapy they are receiving, potential irAEs, and contact numbers for their oncology health care team.
- Assess patient's ability to monitor and report potential irAEs. Engagement of caregiver may be necessary.
- Assess patient for potential for home care support service needs during therapy.
- Educate patient about the potential toxicity profile of ICI therapy, including presenting symptoms and timing.
- Inform patient of exisiting educational resources:
  - Understanding Immunotherapy Side Effects: https://www.nccn.org/images/pdf/Immunotherapy_Infographic.pdf
  - Oncology Nursing Society: Immunotherapy Wallet Cards
  - Society for Immunotherapy of Cancer: Understanding Cancer Immunotherapy, 5th Edition
  - AIM with Immunotherapy: https://aimwithimmunotherapy.org/

**Instruct Patients to Notify the Oncology Health Care Team if:**

- Any new signs or symptoms develop, including severe fatigue, headache, rash, cough, shortness of breath, chest pain, abdominal bloating, change in bowel pattern, weight loss, vision changes or eye pain, severe muscle weakness, severe muscle or joint pains, and/or mood changes.
  - irAEs can occur after completion of therapy. Patients should monitor symptoms for at least 2 years following the conclusion of immunotherapy.
- Patient is evaluated by other HCPs or admitted to the hospital.
- Any new medications are prescribed, or prior to receiving any immunizations or vaccinations.
  - Vaccines that are inactivated or killed preparations are permissible during a course of immunotherapy. Due to the lack of clarity regarding live vaccine use, it is not recommended during ICI therapy.

See Principles of Routine Monitoring for Immune Checkpoint Inhibitors (IMMUNO-1).

Continued

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### PRINCIPLES OF IMMUNOTHERAPY PATIENT EDUCATION

### HEALTH CARE PROVIDER (HCP) INFORMATION (continued)

**Toxicity Management:**

- Review patient medications for potential drug interactions (eg, QT prolongation) when administering agents to manage ICI-related toxicity.
- Mild to moderate adverse events (AEs):
  - Provide symptomatic management.
  - Delay in immunotherapy may be recommended if unclear if irAE is developing or until AEs resolve to grade 1 or pre-treatment baseline.
  - Corticosteroids may be required if AE does not improve. If hormone replacement is required, it is usually for lifetime and may continue beyond the completion of therapy with immune checkpoint inhibitors.
- Severe AEs:
  - Discontinue immunotherapy.
  - Initiate corticosteroid therapy immediately. IV methylprednisolone should be considered until there is evidence of improvement in toxicity.
  - Additional immunosuppressant therapy may be required for steroid-refractory AEs.
  - Inpatient care and additional supportive care may be required.
- Supportive care during immunosuppressant therapy may include the following:
  - Monitoring of blood glucose levels
  - PPIs or H2 blockers to prevent gastritis
  - Antimicrobial and antifungal prophylaxis to prevent opportunistic infections
  - Vitamin D and calcium supplementation to prevent osteoporosis

See Principles of Routine Monitoring for Immune Checkpoint Inhibitors (IMMUNO-1).

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Continued

### PRINCIPLES OF IMMUNOTHERAPY PATIENT EDUCATION

### PATIENT EDUCATION CONCEPTS

- Educational efforts must consider the patient's primary language and literacy level.
- Education should be provided at the start of therapy and at regular intervals as the trajectory of irAEs is variable. Reinforcement of educational concepts is essential.

**Immunotherapy Background:**

- One of the functions of the immune system is to distinguish healthy cells from abnormal cells. Tumor cells have proteins on their surface that bind to immune cells, blocking the ability of the immune cell to recognize them as foreign.
- Immune checkpoint inhibitors are a class of medications that prevent tumors from "hiding" or "evading" the body's natural immune system. Checkpoint inhibitors block the proteins referred to above, "releasing the brakes" on the immune system's white blood cells.
- Immune checkpoint inhibitor (ICI) therapy may be given in combination with other checkpoint inhibitors, chemotherapy, or targeted therapy.

**Side Effects (AEs):**

- AEs from immunotherapy differ from those of other types of cancer treatment and can affect one or several different organ systems.
- Amplifying the immune system can cause T cells to attack healthy cells in the body, causing inflammatory conditions that mimic a range of autoimmune conditions, some of which can be serious. These are known as irAEs.
- irAEs can occur at any time during treatment or after treatment is completed. irAE rebound during steroid taper can also occur, which may impact steroid taper.
- The severity of AEs can range from asymptomatic to severe or life-threatening. They may be cumulative over the course of therapy.
- Combination therapy may increase the severity of AEs. This can occur when immunotherapy is combined with chemotherapy, targeted agents, radiation therapy, or other types of immunotherapy.

**Monitoring and Treatment Response:**

- Therapy with immune checkpoint inhibitor requires close communications between patient/family and the treating center. Symptoms that patients may think are unrelated (for instance, diarrhea or nausea) are often signs of immune checkpoint inhibitor toxicity.
- Educate patients to notify all HCPs (especially primary care providers) that they are receiving/have received immunotherapy.
- Regular monitoring will be conducted to detect any potential irAEs and to assess treatment response.
- Laboratory tests should be obtained prior to each treatment and at regular intervals after completion of immune checkpoint blockade to assess for organ function (eg, complete metabolic panel; kidney, liver, thyroid, pancreas).
- Physical exams will include monitoring of organ function (eg, cardiac, pulmonary, neurologic, skin).
- Asses for significant shifts in weight, as they may be indicative of fluid balance disorders.
- Treatment response time differs from standard cancer therapy; it may take longer to see a response than with other types of cancer therapy.
- Most irAEs can be managed effectively if detected and treated early.

See Principles of Routine Monitoring for Immune Checkpoint Inhibitors (IMMUNO-1).

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## 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).<br>• 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 and symptoms are unresolved, immunotherapy may be resumed while patient is still on ≤10 mg prednisone equivalent daily. Consider concurrent vedolizumab upon resumption of PD-1/PD-L1.<br>• 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.<br>• For grade 3 hepatitis, if on CTLA-4 combined with PD-1/PD-L1, restart with just PD-1/PD-L1 inhibitor.<br>• Permanent discontinuation is warranted in the setting of severe or life-threatening (grade 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.<br>• Permanent discontinuation is warranted for severe (grade 3–4) pancreatitis. |

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Continued

## PRINCIPLES OF IMMUNOTHERAPY RECHALLENGE

**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.<br>• Primary adrenal insufficiency: After appropriate replacement endocrine therapy is instituted, immunotherapy may continue.<br>• 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.<br>• 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.<br>• 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.<br>• Grade 2: Resume once pneumonitis has resolved to ≤ grade 1 and patient is off steroids.<br>• 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.<br>• 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.<br>• 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.<br>• GBS: Permanently discontinue immunotherapy for any grade GBS.<br>• 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.<br>• Aseptic meningitis: Consider resuming following mild to moderate AE if symptoms resolve to grade 0.<br>• Encephalitis: Permanent discontinuation is warranted in the setting of moderate to severe encephalitis (grade 2–4).<br>• Transverse myelitis: Discontinuation of immunotherapy following any-grade transverse myelitis. |
| **Cardiovascular** | • Grade 1 myocarditis: Consider resuming upon resolution of symptoms.<br>• 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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## PRINCIPLES OF PATIENT MONITORING FOR CAR T-CELL–RELATED TOXICITIES

| Before and During CAR T-Cell Infusion | Post-CAR T-Cell Infusion |
|---|---|
| • Perform central venous access, preferably with double or triple lumen catheter, for IV fluid and other infusions in case of toxicities.<br>• Perform cardiac monitoring at least at the onset of grade 2 cytokine release syndrome (CRS) until resolution to ≤ grade 1, clinically significant arrhythmia, and additionally as clinically indicated.<br>• Tumor lysis precautions are recommended for patients with large tumor burden and aggressive histologies, as per standard institutional guidelines.<br>• Start seizure prophylaxis on the day of infusion for CAR T-cell therapies known to cause CAR T-cell–related neurotoxicity (eg, levetiracetam 500–750 mg orally every 12 h for 30 days).<br>• Consider baseline brain MRI. | • Hospitalization or extremely close outpatient monitoring at centers with transplant or prior outpatient CAR T-cell transplant experience. Close monitoring in the hospital is preferable with current products used for adults; however, extremely close outpatient monitoring may be possible at centers with outpatient transplant experience.<br>• Hospitalization for patients with CRS or neurotoxicity is warranted.<br>• Monitor CBC, complete metabolic panel (including magnesium and phosphorus), and coagulation profile.<br>• Baseline CRP and ferritin; recheck at least 3 times per week for 2 weeks post-infusion. Consider daily checks during CRS. CRP can normalize prior to the onset of neurotoxicity.<br>• Assessment for CRS should be done at least twice daily, or when the patient's status changes, during the peak window of CRS risk.<br>• Neurotoxicity assessment should be done at least twice daily or when the patient's status changes, during the peak window of neurotoxicity risk. If neurologic concern develops, assess at a minimum of every 8 hours to include cognitive assessment and motor weakness. |

Overview of CAR T-Cell Therapy-Related Toxicities (CART-2)

**Note: All recommendations are category 2A unless otherwise indicated.**
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## OVERVIEW OF CAR T-CELL THERAPY-RELATED TOXICITIES

| | Axicabtagene ciloleucel[a] and tisagenlecleucel[b] |
|---|---|
| **CRS (CART-3)** | • Typical time to onset: 2–3 days<br>• Typical duration: 7–8 days<br>• Manifestation may include fever, hypotension, tachycardia, hypoxia, and chills. CRS may be associated with cardiac, hepatic, and/or renal dysfunction.<br>• Serious events may include atrial fibrillation and ventricular tachycardia, cardiac arrest, cardiac failure, renal insufficiency, capillary leak syndrome, hypotension, hypoxia, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS). |
| **Neurologic Toxicity (CART-4)** | • Typical time to onset: 4–10 days<br>• Typical duration: 14–17 days<br>• The most common neurologic toxicities include encephalopathy, headache, tremor, dizziness, aphasia, delirium, insomnia, anxiety, and autonomic neuropathy. Agitation, hyperactivity, or signs of psychosis can also occur.<br>• Serious events including seizures, as well as fatal and serious cases of cerebral edema, have occurred. |
| **Hemophagocytic Lymphohistiocytosis/Macrophage-Activation Syndrome (HLH/MAS) During CRS (CART-3)** | • Criteria for considering HLH/MAS:<br>▸ Rapidly rising and high ferritin (>5,000 ng/mL) with cytopenias in the context of CRS, especially if accompanied by ***any of the following***:<br>◊ Grade ≥ 3 increase in serum bilirubin, AST, ALT<br>◊ Grade ≥ 3 oliguria or increase in serum creatinine<br>◊ Grade ≥ 3 pulmonary edema<br>▸ Presence of hemophagocytosis in bone marrow or organs based on histopathologic assessment of cell morphology and/or CD68 IHC. |
| **Miscellaneous** | • Patients may exhibit cytopenias for weeks to months following lymphodepleting chemotherapy and CAR T-cell therapy infusion.<br>• Long-term B-cell aplasia and hypogammaglobulinemia can occur in patients with a complete remission after CAR T-cell therapy infusion. |

[a] Axicabtagene ciloleucel: Median time to CRS onset of 2 days (range: 1–12 days), median duration of 7 days (range: 2–58 days). Median time to neurotoxicity onset of 4 days (range: 1–43 days), median duration of 17 days.
[b] Tisagenlecleucel: Median time to CRS onset of 3 days (range: 1–51 days), median duration of 8 days (range: 1–36 days). Median time to neurotoxicity onset of 6 days (range: 1–359 days); median duration of 14 days.

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## CYTOKINE RELEASE SYNDROME (CRS)[c,d]

- Prompt and urgent intervention to prevent progression of CRS is required; however, other causes of systemic inflammatory response should be ruled out, including infection and malignancy progression. Empiric treatment for infection is warranted in the neutropenic patient. Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.[e]
- Fever is defined as temperature >38°C not attributable to any other cause. In patients who have CRS then receive antipyretics or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

| CRS Grade | Anti-IL-6 Therapy | Corticosteroids[h,i] | Additional Supportive Care |
|---|---|---|---|
| **Grade 1**<br>Fever (≥38°C) | For prolonged CRS (>3 days) in patients with significant symptoms and/or comorbidities, consider tocilizumab as per Grade 2 | N/A | • Empiric broad-spectrum antibiotics, consider granulocyte colony-stimulating factor (G-CSF) if neutropenic[l]<br>• Maintenance IV fluids for hydration<br>• Symptomatic management of organ toxicities |
| **Grade 2**<br>Fever with hypotension not requiring vasopressors and/or hypoxia[f] requiring low-flow nasal cannula[g] or blow-by | Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose).[h] Repeat in 8 hours if no improvement; no more than 3 doses in 24 hours, with a maximum of 4 doses total | For persistent refractory hypotension after 1–2 doses of anti-IL-6 therapy: Dexamethasone 10 mg IV every 6 hours (or equivalent)[j] | • IV fluid bolus as needed<br>• For persistent refractory hypotension after two fluid boluses and anti-IL-6 therapy: Start vasopressors, consider transfer to intensive care unit (ICU), consider echocardiogram, and initiate other methods of hemodynamic monitoring<br>• Manage per Grade 3 if no improvement within 24 hours after starting anti-IL-6 therapy<br>• Symptomatic management of organ toxicities |
| **Grade 3**<br>Fever with hypotension requiring a vasopressor with or without vasopressin and/or hypoxia requiring high-flow cannula,[g] face mask, nonrebreather mask, or Venturi mask. | Anti-IL-6 therapy as per Grade 2[h] if maximum dose not reached within 24-hour period | Dexamethasone 10 mg IV every 6 hours (or equivalent).[j] If refractory, manage as grade 4 | • Transfer to ICU, obtain echocardiogram, and perform hemodynamic monitoring<br>• Supplemental oxygen<br>• IV fluid bolus and vasopressors as needed<br>• Symptomatic management of organ toxicities |
| **Grade 4**<br>Fever with hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation). | Anti-IL-6 therapy as per Grade 2[h] if maximum dose not reached within 24-hour period | Dexamethasone 10 mg IV every 6 hours (or equivalent).[j] If refractory, consider methylprednisolone 1000 mg/day IV[k] | • ICU care and hemodynamic monitoring<br>• Mechanical ventilation as needed<br>• IV fluid bolus and vasopressors as needed<br>• Symptomatic management of organ toxicities |

See Footnotes on next page

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## FOOTNOTES

[c] For HLH/MAS during CRS, treat as per CRS with addition of steroids. If symptoms do not improve within 48 hours, consider etoposide and intrathecal cytarabine for neurotoxicity.

[d] With permission from Elsevier: Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019;25:625-38. DOI: https://doi.org/10.1016/j.bbmt.2018.12.758. This article is published under the terms of the Creative Commons Attribution-NonCommercial-No Derviatives License (CC BY NC ND).

[e] Organ toxicities should receive a thorough workup and appropriate management.

[f] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with a temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

[g] Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/min. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/min.

[h] After each dose, assess need for subsequent dosing.

[i] Antifungal prophylaxis should be strongly considered in patients receiving steroids for the treatment of CRS and/or neurotoxicity.

[j] Alternative steroids at an equivalent dose may be considered.

[k] For example, methylprednisolone IV 1000 mg/day for 3 days, followed by rapid taper at 250 mg every 12 h for 2 days, 125 mg every 12 h for 2 days, and 60 mg every 12 h for 2 days.

[l] GM-CSF is not recommended in the setting of CAR T-cell therapy.

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## CAR T-CELL–RELATED NEUROTOXICITY GRADING

**Immune Effector Cell-Associated Encephalopathy (ICE) Assessment Tool[d]**

- **Orientation: orientation to year, month, city, hospital: 4 points**
- **Naming: ability to name 3 objects (eg, point to clock, pen, button): 3 points**
- **Following commands: ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point**
- **Writing: ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point**
- **Attention: ability to count backwards from 100 by 10: 1 point**

**ICE Scoring**

- **7-9, grade 1**
- **3-6, grade 2**
- **0-2, grade 3**
- **0 due to patient unarousable and unable to perform ICE assessment, grade 4**

**ASBMT Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) Consensus Grading for Adults[d]**

**ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.**

| Neurotoxity Domain[m] | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| **ICE score[n]** | 7-9 | 3-6 | 0-2 | 0 (patient is unarousable and unable to perform ICE) |
| **Depressed level of consciousness[o]** | Awakens spontaneously | Awakens to voice | Awakens only to tactile stimulus | Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma |
| **Seizure** | N/A | N/A | Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention | Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between |
| **Motor findings** | N/A | N/A | N/A | Deep focal motor weakness such as hemiparesis or paraparesis |
| **Elevated ICP/cerebral edema** | N/A | N/A | Focal/local edema on neuroimaging[p] | Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad |

[d] With permission from Elsevier: Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019;25:625-38. DOI: https://doi.org/10.1016/j.bbmt.2018.12.758. This article is published under the terms of the Creative Commons Attribution-NonCommercial-No Derviatives License (CC BY NC ND).

[m] Other signs and symptoms such as headache, tremor, myoclonus, asterixis, and hallucinations may occur and could be attributable to immune effector-cell engaging therapies. Although they are not included in this grading scale, careful attention and directed therapy may be warranted.

[n] A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

[o] Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

[p] Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

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See Treatment on CART-5

## CAR T-CELL–RELATED NEUROTOXICITY TREATMENT

**Assessment and Supportive Care Recommendations (all grades)**
- **Neurologic assessment and grading at least twice a day to include cognitive assessment and motor weakness**
- **MRI of the brain with and without contrast (or brain CT if MRI is not feasible) for ≥ grade 2 neurotoxicity**
- **Neurology consultation at first sign of neurotoxicity**
- **Conduct electroencephalogram (EEG) for seizure activity for ≥ grade 2 neurotoxicity**
- **Aspiration precautions; IV hydration**
- **Use caution when prescribing medications that can cause central nervous system (CNS) depression (aside from those needed for seizure prophylaxis/treatment)**

| Treatment by Grade | No Concurrent CRS | Additional Therapy if Concurrent CRS |
|---|---|---|
| **Grade 1** | • Supportive care | Tocilizumab 8 mg/kg IV over 1 h (not to exceed 800 mg/dose)[r] |
| **Grade 2[q]** | • Supportive care<br>• Dexamethasone 10 mg IV x 1. Can repeat every 6 hours or methylprednisolone 1 mg/kg IV every 12 h if symptoms worsen. | Anti-IL-6 therapy as per Grade 1[r]<br>Consider transferring patient to ICU if neurotoxicity associated with grade ≥2 CRS |
| **Grade 3[q]** | • ICU care is recommended.<br>• Dexamethasone 10 mg IV every 6 h or methylprednisolone, 1 mg/kg IV every 12 h[i]<br>• Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 neurotoxicity. | Anti-IL-6 therapy as per Grade 1[r] |
| **Grade 4[q]** | • ICU care, consider mechanical ventilation for airway protection.<br>• High-dose corticosteroids[i,k]<br>• Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 neurotoxicity.<br>• Treat convulsive status epilepticus per institutional guidelines. | Anti-IL-6 therapy as per Grade 1[r] |

[i] Antifungal prophylaxis should be strongly considered in patients receiving steroids for the treatment of CRS and/or neurotoxicity.
[k] For example, methylprednisolone IV 1000 mg/day for 3 days, followed by rapid taper at 250 mg every 12 h for 2 days, 125 mg every 12 h for 2 days, and 60 mg every 12 h for 2 days.
[q] Diagnostic lumbar puncture for grade 3–4 neurotoxicity; consider for grade 2.
[r] Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.

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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 indicated.

## Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 04/08/19

### Table of Contents

## 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 consisting 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 initial publication of these guidelines in 2018 focused on managing toxicity related to immune checkpoint inhibitor (ICI) therapy. In 2019, the NCCN Guidelines were expanded to address the management of toxicities related to chimeric antigen receptor (CAR) T-cell therapy. These guidelines will be updated at least annually by the collaborative efforts of the panel members based on their clinical experience and available scientific evidence.

## Literature Search Criteria and Guidelines Update Methodology

Prior to the development of this inaugural version of the NCCN Guidelines® for Management of Immunotherapy-Related Toxicities, a search of the PubMed database was performed to obtain key literature on ICI-related toxicity in patients with cancer. The PubMed database was chosen, as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.

The search results were narrowed by selecting studies in humans published in English and their potential relevance was examined. The data from key PubMed articles identified by the panel for review during the NCCN Guidelines update meeting as well as articles from additional sources deemed as relevant to these guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

## The Role of the Immune System in Cancer

Dynamic interactions take place between the immune system and cancer cells, whereby immune cells can detect genetic and cellular abnormalities present on cancer cells. Various mechanisms are in place to closely regulate the activation and function of immune system effectors. However, malignant cells can also modulate immune cell activity, thus evading recognition and destruction by the immune system. This section provides a brief overview of the relationship between the immune system and tumors, and how immunotherapy targets effector cells in the immune system to activate and enhance the antitumor response.

Immunosurveillance refers to the process by which the immune system can screen for, recognize, and respond to foreign pathogens or abnormal (ie, precancerous, cancerous) cells within the body. The theory of cancer immunosurveillance has been incorporated into the larger concept of cancer immunoediting, which details several phases of the interaction between cancer and the immune system: elimination, equilibrium, and

escape. In the elimination phase, a strong response to an immunogenic tumor leads to successful elimination of tumor cells. When the immune system is unable to completely eliminate the tumor, a phase of equilibrium occurs whereby the tumor remains present without progression or metastasis. Persistent equilibrium can lead to the selection of cells that have mutated to resist or avoid the antitumor immune response. This is described as the escape phase, when tumor cells "escape" the antitumor immune response, leading to tumor growth and progression to cancer.[3-7]

Conditions or events that compromise the immune system can lead to cancer cells escaping immunosurveillance.[4,8,9] Once cancer cells have escaped immunosurveillance and have begun to proliferate, their genetic and phenotypic plasticity enable them to develop additional mechanisms by which the tumor can evade, thwart, or even exploit the immune system.[4,8,9]

The immune system is capable of mobilizing immune effector cells in response to cancer cells. Immunotherapies harness the immune system to attack and destroy tumors by regulating molecules involved in immune cell activation. In doing so, immunotherapy seeks to activate or reactivate the antitumor immune response to overcome or circumvent the immune evasion or "escape" mechanisms employed by cancer cells and tumors.

### Evolution of Cancer Immunotherapy

Initial approaches to immunotherapy for cancer are focused on enhancing the immune system's antitumor response by targeting cytokines and other molecules responsible for regulating immune cell activity. Some examples of earlier-generation cancer immunotherapy include interleukin-2 (IL-2) and interferon (IFN) alfa-2b, which have been used to treat malignancies such as melanoma and renal cell carcinoma (RCC). However, a low therapeutic index and suboptimal efficacy limit the use and impact of these agents.[10,11] Lenalidomide and pomalidomide, immunomodulatory agents used for treating multiple myeloma, represent another prior approach to cancer immunotherapy.[12,13] These agents have a complex mechanism of action that results in the costimulation of T cells and NK (natural killer) cells, increased IL-2 and IFN gamma production, and decreased IL-6 and tumor necrosis factor (TNF)-alpha levels, among other effects.[12-14] However, the landscape of cancer care has undergone a dramatic shift with the recent approval of a new generation of cancer immunotherapies during the past 8 years.

Notable new treatments that have recently received FDA approval include ICIs and CAR T-cell therapies. ICIs comprise a novel class of agents that target immune cell "checkpoints," such as programmed cell death-1 (PD-1; eg, nivolumab, pembrolizumab[15,16]) and PD-1 ligand (PD-L1; eg, atezolizumab, avelumab, durvalumab[17-19]), as well as cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4; eg, ipilimumab,[20] tremelimumab [under investigation]). Indications for ICIs have expanded dramatically and now include patients with lung (non-small cell and small cell cancers), head and neck, bladder, kidney, gastric, ovarian, and liver cancers, as well as melanoma, Hodgkin lymphoma, Merkel cell carcinoma, and tumors deficient in DNA mismatch repair mechanisms. ICIs, which were initially indicated for pretreated advanced disease, have moved into earlier treatment settings.[15]

The most recent addition to the cancer immunotherapy armamentarium is CAR T-cell therapy. Current approaches involve CD-19–directed genetic engineering of autologous T cells to enable the patient's immune system to recognize and kill tumor cells. Currently approved CAR T-cell therapies include axicabtagene ciloleucel for diffuse large B-cell lymphomas (DLBCLs) and tisagenlecleucel for B-cell precursor acute lymphoblastic leukemia (ALL) and DLBCL.[21,22]

## Immune Checkpoint Inhibitors

Some of the most effective immunotherapies to date target immune checkpoints exploited by cancers to decrease immune activity. This section will provide a general overview of the mechanism of action of ICIs and discuss what is known regarding ICI-mediated immune dysfunction. For a discussion of the efficacy data for ICIs, please see the NCCN Guidelines for Treatment of Cancer by Site at www.NCCN.org.

### Mechanism of Action

T-cell activation is an essential component of antitumor immunity, requiring costimulation through more than one mechanism. Binding of antigen-specific T-cell receptor (TCR) to major histocompatibility complex (MHC) on antigen-presenting cells (APCs) must be accompanied by costimulatory signals. CD28 is a well-characterized costimulatory factor expressed on T cells. Adequate CD28 binding to B7 family of costimulatory factors (CD80 [B7-1] or CD86 [B7-2]) on APCs is required for T-cell proliferation and full activation. The presence of growth factors such as IL-2 promotes T-cell differentiation and survival.[23,24]

Since unopposed immune activation can lead to a number of tissue-damaging consequences, the immune system has evolved to have complex self-regulatory mechanisms to control or dampen immune responses. This immunologic tolerance is maintained through a variety of mechanisms that include regulatory immune cells, immunosuppressive cytokines and chemokines, and immune checkpoint signaling. Immune checkpoint proteins such as CTLA-4 and PD-1 are closely regulated by immune cells to modulate T-cell activity. When bound by endogenous ligands, these receptors initiate a signaling cascade that suppresses T-cell activation, limiting the immune response. Cancer cells coopt the various mechanisms of immune tolerance, including immune checkpoints to evade recognition by the immune system. Antibodies have been designed to bind these receptors to prevent receptor-ligand interaction, thus removing inhibition of T-cell activation. In doing so, the inhibitory interactions between tumor cells and infiltrating T cells are blocked, reversing T-cell tolerance. This process “releases the brake” on the immune response, promoting the immune system to mount an antitumor response.[25-34]

#### *CTLA-4 Inhibitors*

CTLA-4 is expressed by CD4+ (helper), CD8+ (cytotoxic) T cells, as well as regulatory T cells (Tregs). CTLA-4 functions as an early inhibitory signal during the priming phase for T-cell activation, typically within the lymph nodes. CTLA-4 cell surface expression is upregulated by several factors including TCR activation and certain cytokines. Early studies identified CTLA-4 as a negative regulator of T-cell activation through its high-affinity binding to costimulatory factors of the B7 family (ie, CD80 and CD86) at the surface of APCs. CTLA-4 outcompetes CD28 for binding to costimulatory factors on APCs, acting as a brake on this mechanism for T-cell activation by reducing IL-2 production and T-cell proliferation and survival. The relative degree of signaling through CD28/B7 versus CD28/CTLA-4 determines activation versus anergy of T cells.[23,24,35-38] Subsequent studies revealed the potential role of CTLA-4 blockade in the antitumor response.[39] CTLA-4 blockade results in greater numbers of effector T-cell clones becoming active and proliferating while reducing the immunosuppressive activity of Tregs.[24,40,41]

#### *PD-1/PD-L1 Inhibitors*

PD-1 receptor is present on the cell surface of various immune cells such as T cells, B cells, and NK cells. Its ligands, PD-L1 and PD-L2, have differential tissue expression. PD-L1 is expressed by a wide variety of tissues types, including tumor cells, whereas PD-L2 expression is mainly restricted to hematopoietic cells. PD-1 signaling exerts an inhibitory effect during the effector phase through inhibition of previously activated T cells primarily in the peripheral tissues. It decreases T-cell proliferation through reduced production of IFN-gamma, TNF alpha, and IL-2. In addition to

blocking tumor cell apoptosis, PD-1 interaction with PD-L1/2 can lead to the progressive loss of T-cell functions (ie, T-cell exhaustion) and drive the conversion of T effector cells to Treg cells with immunosuppressive properties.[24,42-47] Studies have implicated PD-1 signaling in the antitumor response.[48] Blockade of the PD-1/PD-L1 interaction can lead to the reactivation of T-cell populations that have become exhausted following prolonged antigen exposure, such as quiescent antitumor T cells.[24,43,49]

### ICI-mediated Immune Dysfunction

The pharmacodynamics and pharmacokinetics of ICI immunotherapy differ greatly from that of cytotoxic chemotherapy or targeted anti-cancer therapy.[50] Similarly, anti-CTLA-4 and anti-PD-1/PD-L1 immunotherapies are associated with toxicity profiles that are distinct from those observed with conventional anti-cancer therapies, though their presentation may at times be similar.[51-57] Whereas traditional cytotoxic chemotherapy often results in acute-onset emetic and myelosuppressive effects, irAEs tend to be relatively delayed-onset and inflammatory or autoimmune in nature.[58-61]

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 spectra of irAEs associated with blockade of immune checkpoints falls in line with the phenotypes observed as a result of mutations in the genes encoding CTLA-4 and PD-1 and has considerable overlap across the various ICIs.[62-65]

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-17).[64,66] One potential mechanism is T-cell activity directed at antigens present in both tumor cells and healthy tissue.[67,68] Inflammation in otherwise normal tissues could result from elevated levels of inflammatory cytokines as a downstream effect of T-cell activation.[69-72] 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.[73,74] Finally, immunotherapy might increase the levels of preexisting autoreactive antibodies.[75]

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; much 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%.[1,76] Severe irAEs

requiring immunosuppression and hold or discontinuation of treatment are estimated between 0.5% and 13% for monotherapy.[76] Analysis of pooled trial data found that 43% of patients discontinued combination therapy (nivolumab/ipilimumab) due to AEs, with gastrointestinal (GI) events being the most commonly reported reason for discontinuation.[77] ICI immunotherapies have been associated with rare AEs that are still in the process of being identified and studied at high-volume centers.

***Single-Agent Therapy***

***CTLA*-4**

A 2015 meta-analysis by Bertrand, et al examined data from 1265 patients across 22 clinical trials of anti–CTLA-4 antibodies (ipilimumab [n = 1132] and tremelimumab [n = 133]), reporting an overall incidence of 72% for any-grade irAEs and 24% for high-grade irAEs.[78] 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).[79] 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.[79] 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%).[80,81]

**PD-1/PD-L1**

For PD-1/PD-L1 inhibitors, the reported overall incidence of any-grade irAEs was up to 30% based on patients in phase III trials.[1,82-84] To date, the incidence of high-grade AEs associated with PD-1/PD-L1 inhibitors appears to be somewhat less dose-dependent than ipilimumab and to vary by disease site.[76] 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.[85] Rates of high-grade irAEs were similar across pembrolizumab, nivolumab, and atezolizumab, ranging from 5% to 8%.[85]

De Velasco and colleagues recently reported on the incidence of the most common ICI-associated irAEs in a meta-analysis of 21 randomized phase II/III trials conducted from 1996 to 2016, which included a total of 6528 patients who received monotherapy (atezolizumab, n = 751; ipilimumab, n = 721; nivolumab, n = 1534; pembrolizumab, n = 1522) and 4926 patients in placebo or standard therapy control arms using chemotherapy or biologic agents.[86] 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 (AST elevation), rash, hypothyroidism, and pneumonitis. When compared to 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.[86] In a separate review of the data, Kumar and colleagues also compared the risk of developing certain irAEs with different classes of ICIs.[76] While 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.[76]

De Velasco, et al 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.[86] Khoja, et al also conducted a systematic review of irAEs by ICI class and tumor type in 6869 patients from 48 trials between 2003 and 2015,[87] with probable considerable overlap in patient population from the De Velasco study. Although most findings were similar, Khoja and colleagues' 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 NSCLC. Patients with melanoma experienced arthritis and myalgia more commonly than those with RCC, but patients with RCC experienced 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 since the majority of available data was on patients with melanoma.[87]

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 non-small cell lung cancer (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 = 3284; PD-L1: n = 2460).[88] 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* = 0.4). 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).[88] Similar findings were reported in a 2017 meta-analysis of data on pneumonitis incidence with PD-1 inhibitors (12 trials, n = 3232) and PD-L1 inhibitors (7 trials, n = 1806).[89] 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).[89]

***Combination Therapy***

Numerous ongoing studies are examining regimens that include ICIs given in combination with another ICI, chemotherapy, or targeted agent. While 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.[90-92] 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.[93-96]

The only current FDA-approved regimen using combined ICI therapy is nivolumab plus ipilimumab for treating advanced melanoma, RCC, or microsatellite-unstable tumors.[16,20] Nivolumab plus ipilimumab resulted in enhanced survival outcomes compared with ipilimumab monotherapy in advanced melanoma.[92,97] 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 the survival benefit, as evidenced by a 3-year survival rate of 67%.[92]

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.[98] Dose-modified nivolumab plus ipilimumab regimens are also under investigation for NSCLC and small cell lung cancer (SCLC),[99,100] and nivolumab plus ipilimumab is recommended by 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.[101-103] Immune checkpoint blockade given in combination with radiation therapy is also the subject of investigation.[104,105]

### ICI Therapy-Related Fatal irAEs

A recently published systematic review and meta-analysis examined fatal irAEs from ICI therapy using data from multiple sources.[91] 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 reported for anti-CTLA-4 monotherapy (1.08%) and anti-PD-1/PD-L1 + 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.[91]

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.[91] 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.[91]

Finally, temporal patterns of fatal irAEs were examined using combined pharmacovigilance case reports and multicenter retrospective data review.[91] 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.[91]

### 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 outcomes is provided below. 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.[106] A retrospective review found that cutaneous irAEs,

particularly vitiligo, may be associated with improved treatment response with pembrolizumab.[107-109] In patients with melanoma who received nivolumab, rash and vitiligo were both associated with improved overall survival (OS).[110] 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.[111]

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%; $P < .0001$).[112] 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.[113]

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).[114] 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 examined pooled data from randomized phase II/III trials in which patients received combination nivolumab plus ipilimumab therapy (n = 409).[77] Therapy was discontinued due to AEs in 176 patients, including 96 patients who discontinued therapy during the induction phase (in which the majority of 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.[77]

## 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 for most high-grade irAEs. Importantly, short-term use of corticosteroids to treat irAEs has not been shown to reduce anti-tumor efficacy. Appropriate duration and careful taper of corticosteroid therapy is important to prevent the recurrence of irAEs. 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 non-steroid 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 managing steroid-refractory or severe irAEs are discussed below.

TNF inhibitors are a class of drugs widely used to block the inflammatory effects of TNF in autoimmune diseases.[115] 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.[115-117] Infliximab blocks the interaction of TNFα with its receptors, inhibiting induction of pro-inflammatory cytokines (IL-1, IL-6) and modulating the activity of immune effectors such as leukocytes, neutrophils, and eosinophils.[117,118] Infliximab has become a commonly used agent for treating steroid-refractory irAEs that develop during ICI therapy.[64,119] For patients with severe irAEs not responsive to steroids within 48 to 72 hours, early initiation of anti-TNFα therapy (ie, at 72 hours) may be warranted in consultation with the relevant medical specialist. Duration of therapy with TNF-alpha blockers for irAEs is not clearly defined, but is typically a single dose. A second dose of anti-TNFα therapy may be required, and can be administered 2 weeks after initial dose of infliximab. Anti-TNFα agents (eg, infliximab) are particularly effective in management of immune-related colitis and inflammatory arthritis (IA).

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 GI tissues. Vedolizumab is currently indicated for treating GI inflammation due to ulcerative colitis and Crohn's disease.[120,121] Case reports have described the use of vedolizumab for treating ICI-induced enterocolitis.[121,122] Vedolizumab may provide more specific immune suppression for the inflamed GI mucosa, hence theoretically sparing systemic immune suppression and anti-tumor 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 (MPA) or as mycophenolate mofetil (MMF), a prodrug of MPA.[123,124] These agents have multiple immunosuppressive actions, which result in decreased B- and T-cell proliferation, T-cell apoptosis, and suppression of dendritic cells and IL-1.[125,126] Published studies also support the clinical efficacy of these mycophenolate in various inflammatory or autoimmune conditions, such as autoimmune hepatitis, myositis, bullous disease, interstitial lung disease, and lupus nephritis, among others.[127-132] 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.[90,133-136]

Intravenous immunoglobulin (IVIG) has been used to suppress a wide array of autoimmune and chronic inflammatory conditions.[137,138] It is comprised of pooled IgG immunoglobulins harvested from the plasma of healthy blood donors and prepared for intravenous (IV) 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.[138-140] 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.[141,142]

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.[143] Plasmapheresis (and IVIG) is often indicated as a second-line therapy for managing neurologic irAEs after limited or non-response to initial high-dose corticosteroid.[144] However, success in treating severe and often rapidly progressive neurologic irAEs has been mixed.[144-146]

Additional agents that have been used less frequently as part of advanced lines of immunosuppressive 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.[147-152] 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 [NSAIDS] or anticoagulants), histamine 2 (H2) blockers or proton pump inhibitors can be given during steroid therapy. Consider prophylactic antimicrobial and antifungal agents. Prophylaxis against pneumocystis jiroveci pneumonia (PJP) 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. Lastly, 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 (TB).[153-156] The panel recommends testing for hepatitis B and C virus prior to TNF inhibition, and carriers should be monitored during and for several months after immunosuppressive therapy. Additionally, testing for latent/active TB is recommended prior to initiation of infliximab therapy; IFN-gamma release assays are preferred. However, TB testing should not delay initiation of anti-TNFα 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 initiated 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 nivolumab for advanced melanoma.[157] 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.[157] Similar findings were reported by an earlier retrospective analysis of 298 patients with metastatic melanoma who were treated with ipilimumab.[114] Within this cohort, 103 (35%) required corticosteroid therapy to manage irAEs, and 29 of these patients (10%) also required anti-TNF alpha 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.[114] 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.[77,158]

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.[77] Another analysis of pooled data from these

trials demonstrated similar survival outcomes between patients with GI irAEs who received corticosteroid therapy ± infliximab and patients with GI irAEs who did not receive immunosuppressive agents.[158]

Due to clinical trial exclusion criteria, less is known about the impact of immunosuppressants on ICI efficacy when given prior to 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 (PFS), and OS.[159] Additional research will be needed to better understand the potential impact of corticosteroid exposure prior to or during ICI therapy initiation, especially as it pertains to premedication with corticosteroid prior to ICI infusion.

### 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 preexisting 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%.[160-162] 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.[163] Preliminary data on safety and toxicity are described below.

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.[162] 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 preexisting 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.[162]

Studies have also examined the effects of PD-1 inhibitors for advanced melanoma in patients with pre-existing autoimmune disease.[160,161] Among a subset of 19 patients with prior autoimmune disease, PD-1 inhibition led to autoimmune flare in 42%, and onset of a new irAE in 16%.[160] 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.[161] Interestingly, no members of that cohort with GI or neurologic autoimmune conditions (n = 11) experienced a flare.[161] In both studies of PD-1 inhibitors, most flares of preexisting autoimmune conditions were adequately managed using immunosuppressive and symptomatic therapy.[160,161] However, onset of new irAEs led to discontinuation of PD-1 inhibitor in about 10% of patients in one study.[161]

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.[160,161,164] Among the 22 patients with ipilimumab-related irAEs described by Gutzmer et al, treatment with a PD-1 inhibitor led to a flare of the prior irAE in 4.5% of patients, while 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.[161]

Nivolumab or pembrolizumab monotherapy was resumed in a cohort of 80 patients who had previously discontinued combination ICI therapy due to irAEs.[164] Upon resumption of PD-1 inhibitor, 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 rechallenge (21%), the authors posited two 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.[164] Additional research is needed to understand the safety of ICI therapy in this population and others at a potentially greater risk for developing irAEs.

NCCN Recommendations

Optimization of immunosuppression for pre-existing autoimmune conditions and close cooperation with pertinent subspecialists is recommended. These guidelines suggest a goal of immunosuppressive regimen allowing for prednisone dose of <10 mg daily (or equivalent) prior to initiating cancer immunotherapy. However, patients with autoimmune neurologic conditions or life-threatening autoimmune disorders are unlikely to be suitable candidates for ICI immunotherapy. Additionally, ICI therapy may not be appropriate for patients whose autoimmune conditions are inadequately controlled using immunosuppressive medications, or for those who require high doses of immunosuppressive agents to manage their condition.

Caution should be exercised when considering resumption of ICI therapy for patients who have experienced a previous treatment-related irAE. A key consideration is the patient’s tumor response. In patients with responding or stable disease, it may be prudent to continue close surveillance and to re-introduce ICI therapy if the patient develops evidence of progression of cancer. As appropriate, consult with organ-specific specialists prior to resumption. With some exceptions, resumption of ICI therapy after a grade 2 irAE can be considered once signs and symptoms have resolved to grade 1 or below. Perform close follow-up to monitor for any signs or symptoms of irAE recurrence. If toxicity returns upon ICI rechallenge, permanently discontinue that class of ICI.

In the setting of most severe (and some moderate) irAEs, permanent discontinuation of that given class of immunotherapy is typically warranted. For example, if a patient experiences grade 3 or 4 toxicity from an ipilimumab-containing regimen, consideration may be given to later therapy with anti-PD-1/PD-L1 monotherapy upon full resolution of any earlier toxicity.

***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.[165] 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.[165-168] 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.[165] 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.[165,169] 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.[165,166]

Research is underway to explore alternative immunosuppressive regimens in an effort to reduce allograft rejection during ICI therapy.[166,169] 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 observed for treatment arms in which pembrolizumab was added to lenalidomide/dexamethasone or pomalidomide/dexamethasone.[170]

NCCN Recommendations

Consideration of ICI therapy in organ transplant recipients is very complex and requires multidisciplinary involvement. Graft failure while on ICI immunotherapy has been reported, and transplant organ loss may be an outcome of treatment. Patients with solid organ transplantation who have a viable option for alternative therapy if graft rejection occurs (ie, kidney and dialysis) may be candidates for immunotherapy, particularly if there is no prior evidence of graft rejection and patients are on a stable maintenance immunosuppression regimen. The possible consequences of ICI therapy should be discussed with the patient and organ transplant team and there should be a plan in place to seamlessly manage the patient if graft loss occurs. Although patients with prior allogeneic stem cell transplant may be candidates for immunotherapy, there is an increased risk of transplant-related complications, including potentially fatal graft-versus-host disease (GVHD). Careful discussion with the patient and stem cell transplant physicians should precede initiation of immunotherapy.

### 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 management of complex cases or multi-system 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.[171,172] irAE rebound during steroid taper has also been reported. The typical timing and presentation of specific irAEs are discussed below. 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 following significant toxicity. Clinicians should 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. 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 (439/1738) with high-

grade events in 0.7% (12/1738); the majority occurred during the first infusion, with nearly all reactions occurring within the first 4 treatment cycles.[17,173] Premedication appeared to decrease the rate of severe infusion-related reactions (IRRs).[173] The U.S. prescribing instructions for avelumab include acetaminophen and diphenhydramine prior to infusion during the first 4 treatment cycles.[17]

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.[1,15,16,18-20]

NCCN Recommendations

The panel refers clinicians to the prescribing information for each individual immunotherapy agent for recommendations regarding premedication to prevent infusion reactions. In the absence of specific indications such as prior IRR or concurrent chemotherapy, routine premedication with corticosteroids prior to receiving ICI therapy is not recommended given the potential mitigation of immunotherapeutic effectiveness in the prophylactic setting.

In patients having a possible IRR, perform a physical examination, monitor vital signs, monitor pulse oximetry, and perform an ECG if the patient is experiencing chest pain or sustained tachycardia. Symptoms of IRRs can include fever, chills, rigors; urticaria/pruritus; angioedema; flushing; headache; hypertension or hypotension; and/or shortness of breath, cough, or wheezing. Hypoxemia, dizziness/syncope, sweating, and arthralgia or myalgia may also occur.

Mild (G1) reactions are typically transient and do not require immunotherapy infusion interruption or other intervention. For moderate (G2) reactions, hold or slow the rate of infusion and treat per institutional guidelines. Antihistamines, acetaminophen, NSAIDS, narcotics, or IV fluids may be required. Moderate reactions typically respond promptly to symptomatic treatment and require medication for ≤24 hours. Consider premedication with acetaminophen and diphenhydramine with future infusions. For severe (G3/4) IRRs, treat urgently according to institutional guidelines. Permanently discontinue the immune checkpoint drug(s) associated with the toxicity. Severe reactions are often more prolonged with limited responsiveness to intervention or infusion interruption. Symptoms can reoccur following initial improvement. Inpatient care and urgent intervention may be needed to prevent life-threatening consequences.

***Dermatologic Toxicity***

Dermatologic toxicities are the most prevalent irAEs associated with ICI therapy. Inflammatory skin conditions typically present within the first 2 cycles of treatment (ie, within several weeks).[51,83,86,174,175] 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%–70% for ipilimumab and 17%–40% for PD-1/PD-L1 inhibitors. The rates of high-grade dermatologic irAEs are similar across ICI classes and range from 1%–3% for ipilimumab and PD-1/PD-L1 inhibitors.[2,76,83,176] 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.[177]

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.[51,174,177,178] Alopecia and hair repigmentation

have also been reported.[177,179,180] 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 (SJS/TEN) and drug rash with eosinophilia and systemic symptoms (DRESS) have been reported.[178,181,182] Although serious conditions typically required hospitalization, resolution was achievable via systemic immunosuppressive therapy and ICI discontinuation.

NCCN Recommendations

To assess potential dermatologic irAEs, the guidelines recommend total body skin exam, including mucosa, and patient history of any prior inflammatory dermatologic disease. Routine examination of skin and mucosa is recommended for patients with a history of immune-related skin disorders. Clinicians should monitor the lesion type and affected body surface area (BSA); photographic documentation may be helpful. Biopsy can be considered for rash with unusual features. Treatment recommendations are subdivided by presentation into maculopapular rash, pruritus, and bullous dermatitis (blistering disorders). In general, short-term use of higher potency topical corticosteroids (eg, Class 2 or 3) is preferred over longer-term use of a lower-potency agent.

Maculopapular rash is characterized by the presence of macules (flat) and papules (elevated). Also known as morbilliform rash, it is one of the most common cutaneous AEs, frequently affecting the upper trunk, spreading centripetally, and may be associated with pruritus. Oral antihistamine and topical emollient are recommended. Mild (G1) maculopapular rash should be treated with moderate-potency topical corticosteroid while ICI therapy continues. For moderate rash (G2), treatment with high-potency topical corticosteroids and/or 0.5–1 mg/kg/day prednisone is indicated. Consider holding immunotherapy. For severe rash (G3/4), hold immunotherapy and treat with high-potency topical corticosteroids and 0.5–1 mg/kg/day prednisone (with dose increase up to 2 mg/kg/day if no improvement). Urgent dermatology consultation is recommended; consider inpatient care. Following immunotherapy hold, consider resuming once symptoms have resolved to ≤ G1 and only topical interventions are indicated.

Pruritus is an intense itching sensation that may occur with or without rash. Mild pruritus (G1) can be treated with oral antihistamines and moderate-potency topical corticosteroid while immunotherapy is continued. Consult dermatology and continue immunotherapy with intensified antipruritic therapy for moderate pruritus (G2). Immunotherapy hold can be considered in select cases. Oral antihistamines are recommended in addition to high-potency topical steroid. For severe pruritus, hold immunotherapy and obtain urgent dermatology consultation. In addition to antihistamines, oral or IV prednisone/methylprednisolone (0.5–1 mg/kg/day) should be administered. Consider a GABA antagonist such as gabapentin or pregabalin, and aprepitant or omalizumab for refractory cases. Following immunotherapy hold, consider resuming once symptoms have resolved to ≤ G1 and only topical intervention is required.

Bullous dermatitis and other forms of blistering skin reactions are characterized by skin inflammation and fluid-filled bullae. For mild to moderate bullous dermatitis, hold immunotherapy until resolution. High-potency topical corticosteroid (G1) or 0.5–1 mg/kg/day prednisone/methylprednisolone (G2) is indicated. For severe or life-threatening bullous dermatitis and all cases of SJS/TEN, hospitalization and permanent discontinuation of immunotherapy are required. Seek urgent consultation from dermatology, ophthalmology, and urology. Methylprednisolone/prednisone should be initiated at 1–2 mg/kg/day.

In cases for which systemic corticosteroid is indicated, treatment should be continued until symptoms improve to ≤ G1, followed by dose taper over 4 to 6 weeks.

***Gastrointestinal (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.[183,184] 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%.[76,185] The highest rates of ICI-mediated GI irAEs have been observed with the addition of a PD-1/PD-L1 inhibitor to CTLA-4 blockade.[186-188] Retrospective case reviews suggest that symptom grade may not correlate with colitis severity as observed by endoscopy and histology.[111,189]

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 8863 patients with solid tumors examined the incidence of GI irAEs with various ICIs.[188] The highest rates of GI irAEs were observed 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).[188] Another meta-analysis compared the pooled incidence of diarrhea and colitis for different checkpoint inhibitors in patients with melanoma (CTLA-4: n = 3116; PD-1 inhibitors: n = 1537). PD-1 inhibitors were associated with a lower relative risk of all-grade diarrhea and colitis compared with anti–CTLA-4 agents, while 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.[187]

Corticosteroids are typically the first line of treatment for GI irAEs. In retrospective reviews of patients with ICI-related enterocolitis, symptoms resolved with corticosteroid treatment in approximately 40% to 60% of individuals.[184,189,190] 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 to short-duration steroid plus infliximab, suggesting that earlier non-steroid immunosuppressive therapy may confer better outcomes.[111]

Endoscopy revealed colonic ulcerations more commonly in steroid-refractory cases.[184,189,190] Case studies report on the successful use of infliximab for treating severe, steroid-refractory colitis associated with ipilimumab.[190-192] Case series and reports have also documented successful treatment of ICI-mediated, steroid-dependent, or steroid-refractory enterocolitis with vedolizumab.[121,193] Vedolizumab may be effective in the setting of infliximab-resistant inflammation of the small intestine and colon.[122]

NCCN Recommendations

Determine the patient's baseline bowel habits. 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. For patients presenting with mild diarrhea (G1), close monitoring is recommended with progressive symptoms indicating further workup. Loperamide or diphenoxylate/atropine and hydration are recommended, and consider holding immunotherapy. Moderate (G2) or severe (G3/4) diarrhea and colitis require stool evaluation to rule out infectious etiology. Consider abdominal/pelvic CT with contrast and GI consultation for further evaluation (ie, colonoscopy or flexible sigmoidoscopy ±

esophagogastroduodenoscopy [EGD] with biopsy). Therapy for irAE can be initiated while awaiting test results.

For moderate diarrhea/colitis (G2), hold immunotherapy and administer prednisone/methylprednisolone (1 mg/kg/day). If no improvement is noted within 2 to 3 days, increase corticosteroid dose to 2 mg/kg/day and consider adding infliximab. Consider inpatient care if needed to provide adequate supportive care for severe colitis (G3/4). Administer IV methylprednisolone, 2 mg/kg/day. If no response is detected in 2 days, continue steroids and consider adding infliximab. Consider vedolizumab for infliximab-refractory diarrhea and colitis or cases for which infliximab is contraindicated.

For patients taking ipilimumab, the panel recommends permanent discontinuation if a serious or life-threatening GI irAE occurs. For patients receiving PD-1/PD-L1 inhibitors, therapy should be held for G2/3 irAEs, with consideration of rechallenge upon resolution of symptoms below G1. For rare circumstances in which the patient cannot completely taper off corticosteroids, immunotherapy may be resumed while the patient is still on ≤10 mg prednisone (or equivalent) daily. Permanently discontinue the immunotherapy agent(s) responsible for the toxicity after G4 irAEs. If a systemic corticosteroid is given, treatment should be continued until symptoms improve to ≤ G1, followed by dose taper over 4 to 6 weeks. Convert from IV methylprednisolone to oral prednisone when appropriate.

***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.[65] Asymptomatic elevations in aspartate transaminase (AST) and alanine transaminase (ALT) are the most commonly observed hepatic AEs.[57,176] 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.[194] Combination therapy is associated with a considerably higher incidence of hepatotoxicity with 29% and 17% experiencing any-grade and high-grade hepatotoxicity, respectively.[194,195] Median time of onset is typically 5 to 6 weeks from start of treatment but irAEs can occur months later.[194,196-198] 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.[199,200] A recent study characterized the distinct histologic patterns associated with hepatitis mediated by CTLA-4 versus PD-1/PD-L1 blockade.[196]

Corticosteroids are the most common method of treatment in most studies of ICI-mediated hepatotoxicity.[194,196,197] In several cases, re-initiation of steroids after taper was needed based on worsening liver values.[197] Mycophenolate has been used to treat severe persistent hepatitis despite corticosteroid therapy.[136,194,201,202] Another study reported the use of cyclosporine as an additional immunosuppressant in the setting of steroid-refractory hepatotoxicity.[197] 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.[203,204]



NCCN Recommendations

Liver damage may be indicated by elevated levels of the liver enzymes ALT and AST (ie, transaminitis). Patients experiencing hepatic irAEs may present with varying grades of transaminitis. The panel recommends ruling out other potential factors such as viral etiology, disease-related hepatic dysfunction, or drug-induced enzyme elevations. Specialist consultation should be considered and efforts should be made to limit or discontinue any hepatotoxic medications. Assess acetaminophen, dietary supplement, and alcohol use.

Treatment recommendations are separated based on the co-occurrence of elevated bilirubin. Management of transaminitis without elevated bilirubin

is by grade, based on the degree to which enzymes exceed the upper limit of normal [ULN]). For mild transaminitis (G1), immunotherapy can be continued with increased frequency of transaminase and bilirubin monitoring. Consider holding immunotherapy for concerning laboratory value trends. Hold immunotherapy for moderate transaminitis (G2) and monitor liver function tests (LFTs) every 3 to 5 days and consider prednisone 0.5–1 mg/kg/day. Severe or life-threatening transaminitis (G3/4) requires permanent discontinuation of ICI therapy, hepatology consult, and LFT monitoring every 1 to 2 days. Provide inpatient care for G4 transaminitis and consider hospitalization for G3. Liver biopsy can be considered if there are no contraindications. Initiate prednisone at 1–2 mg/kg/day (G3) or 2 mg/kg/day (G4). For patients with persistent severe hepatitis despite high-dose corticosteroid for 3 days, consider adding MMF. Infliximab is not currently recommended for use in patients with hepatitis.

For ≥ G2 transaminitis with bilirubin levels above 1.5 ULN (excluding patients with Gilbert's syndrome), management is similar to that for high-grade hepatitis without bilirubin elevation. Permanently discontinue immunotherapy and initiate prednisone at 2 mg/kg/day. Monitor LFTs daily and consult with hepatology. Mycophenolate can be considered in addition to steroid for refractory cases after 3 days.

For all hepatitis cases requiring corticosteroid, initiate tapering when liver enzymes show sustained improvement or return to ≤ G1. Continue to taper dose over at least 1 month with re-escalation as needed for rebounding enzyme levels. In the setting of G2 hepatis without elevated bilirubin, clinicians can consider resuming immunotherapy once liver enzymes return to baseline and prednisone (or equivalent) has been tapered to ≤10 mg daily. Do not rechallenge following high-grade (G3/4) irAEs.

***Pancreatic Toxicity***

Amylase and/or lipase elevations, although typically asymptomatic, can occur with ICI therapy. The potential significance of asymptomatic elevations remains unclear, but discontinuation of therapy is not usually recommended based on these findings alone.[76,176,205] Although rare, acute pancreatitis has been observed in patients taking ICIs,[176,199,206] and radiologic features of immune-related pancreatitis have been described.[207] Cases of recurrent pancreatitis have been reported upon resumption of PD-1 inhibitors following a hold for initial irAE.[164] 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.

NCCN Recommendations

Baseline/routine amylase/lipase assessments and pancreatic imaging do not need to be performed outside of clinical suspicion of pancreatitis. For persistent moderate/severe elevations in amylase and/or lipase, the panel recommends evaluation for pancreatitis to include clinical assessment and imaging. Imaging may include abdominal CT with contrast or magnetic resonance cholangiopancreatography (MRCP). Other potential causes for elevated pancreatic enzymes should be considered. For moderate/severe elevations in amylase and/or lipase, consider continuing immunotherapy if no evidence of pancreatitis is found.

Provide standard medical care for signs and symptoms of acute pancreatitis, including hospital admission, aggressive fluid resuscitation, and pain control. Gastroenterology consultation and immunosuppression are warranted if clinical assessment and/or imaging findings support moderate/severe acute pancreatitis. For moderate (G2) pancreatitis, hold immunotherapy and initiate methylprednisolone/prednisone at 0.5 to 1 mg/kg/day. Permanently discontinue ICI therapy for severe (G3/4) pancreatitis and administer corticosteroid at 1–2 mg/kg/day.

In cases for which systemic corticosteroid is indicated, treatment should be continued until symptoms improve to ≤ G1, followed by dose taper over 4 to 6 weeks. If there is no evidence clinical/radiologic evidence of pancreatitis and amylase/lipase levels improve, clinicians can consider resuming immunotherapy after a hold for a symptomatic G2 irAE. Consider consulting with a pancreatic specialist regarding rechallenge. Resumption of immunotherapy is not recommended after G3/4 pancreatitis.

***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 and Byun, et al.[208,209] 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) in order to tailor management appropriately.[208,209] 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 have reviewed imaging features of endocrine irAEs at presentation and after treatment to assist in making a differential diagnosis.[210]

Different patterns of endocrine dysfunction have been observed with various ICI regimens. Hypophysitis is characteristic of ipilimumab, while 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.[1,208,209,211] 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.[183,209]

A 2018 meta-analysis examined the incidence of endocrine dysfunction across 38 randomized trials enrolling 7551 patients who received monotherapy with PD-1 inhibitor, PD-L1 inhibitor, or CTLA-4 inhibitor; or combination anti-PD-1/CTLA-4 therapy.[211] 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 to 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.[211]

A retrospective review identified 27 cases of new-onset insulin- dependent diabetes from a population of 2960 patients that received ICI therapy over 6 years at 2 academic medical centers (0.9% prevalence).[212] 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.[212] However, further research will be needed.

ICI-mediated endocrine toxicity often results in permanent organ damage and typically requires life-long hormonal supplementation.[209,213-215] To date, evidence does not suggest that high-dose corticosteroid therapy 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.[208,209,213,215,216]

NCCN Recommendations

***Thyroid Dysfunction***

Thyroid function should be assessed by monitoring the levels of thyroid-stimulating hormone (TSH) and free thyroxine (T4). In the setting of thyroid abnormalities, routine monitoring is recommended every 4 to 6 weeks. This interval can be extended to every 12 to 18 weeks in patients who have normal thyroid function or who continue to be asymptomatic. Evaluation of total T3 is recommended in the setting of abnormal findings.

For asymptomatic or subclinical hypothyroidism, defined as elevated TSH with normal free T4, continue routine monitoring and proceed with immunotherapy. Levothyroxine can be considered for TSH levels above 10 mIU/L. Primary hypothyroidism is characterized by elevated TSH levels (>10 mIU/L) and low free T4 with clinical symptoms. Provide thyroid supplementation and consider endocrine consultation. Prior to starting thyroid replacement therapy, concomitant adrenal insufficiency should be ruled out by testing AM cortisol levels. Low or suppressed TSH with inappropriately low free T4 may present as a sequela of hypophysitis, in which other pituitary axes may be affected. Follow free T4 for thyroid replacement in the setting of hypophysitis-induced loss of TSH production.

Although rare, thyroiditis (often a painless, transient inflammatory process) can occur with ICI therapy. Thyrotoxicosis, observed as low or suppressed TSH (<0.01 mIU/L) with high free T4 and/or total triiodothyronine (T3), may be symptomatic in the setting of high free T4. If symptomatic (eg, palpitations, anxiety, insomnia), consider endocrine consultation and propranolol to manage symptoms until resolution. Thyrotoxicosis often evolves to hypothyroidism. Repeat thyroid function testing should be performed in 4 to 6 weeks. Findings of persistent suppressed TSH with high free T4/total T3 should be followed by additional testing for true hyperthyroidism and Graves' disease-like etiology. Hypothyroidism usually ensues after an occurrence of ICI-induced thyrotoxicosis. If TSH becomes significantly elevated (>10 mIU/L), thyroid supplementation should be initiated.

Immunotherapy may be continued in the setting of hypothyroidism or thyrotoxicosis. When appropriate, levothyroxine is given for thyroid hormone supplementation at approximately 1.6 mcg/kg with the intent of getting TSH levels to reference range or age-appropriate values. Levothyroxine dose can be reduced by 10% to avoid hyperthyroidism in patient populations that may be sensitive to thyroid supplementation (ie, elderly or patients with comorbidities). The guidelines recommend TSH and T4 monitoring every 4 to 6 weeks during immunotherapy, with follow-up every 12 week thereafter, as indicated.

*Hypophysitis*

Acute symptoms of hypophysitis can include headache, photophobia, dizziness, nausea/emesis, fevers, anorexia, visual field cuts, or severe fatigue. Chronic symptoms can include fatigue and weight loss. Workup for hypophysitis should include assessment of adrenocorticotropic hormone (ACTH), AM cortisol, follicle-stimulating hormone (FSH),

luteinizing hormone (LH), TSH, free T4, testosterone in men, and estrogen in premenopausal women. Test results indicative of hypophysitis may show low levels of the following: ACTH, AM cortisol, sodium, potassium, testosterone, and DHEA-S. If the patient is symptomatic, a brain MRI with pituitary/sellar cuts is recommended.

Consider consulting endocrinology if a diagnosis of hypophysitis is made. For acute, symptomatic hypophysitis (headache and symptoms that are caused by acute swelling of the pituitary), hold immunotherapy and initiate methylprednisolone/prednisone at 1–2 mg/kg/day until acute symptoms resolve, typically 1 to 2 weeks. Then taper steroids rapidly to physiologic replacement levels upon improvement. Consider resumption of ICI therapy once symptoms related to mass effect have resolved.

The more common presentation for hypophysitis features deficiency of TSH/ACTH and/or gonad-stimulating hormones, but without symptomatic pituitary swelling. Patients may manifest a variety of symptoms related to deficiency of endogenous thyroid hormone, cortisol, or gonadal hormones. Immunotherapy can be continued while endocrine therapy is titrated to appropriate physiologic levels.

Physiologic hormone replacement will likely be required indefinitely (typically life-long), and should include steroid replacement, levothyroxine if accompanied by central hypothyroidism, and testosterone supplementation in males. Provide patient education regarding stress doses of hydrocortisone in the event of infection, trauma, or other medical event. Patients should wear a medical alert bracelet.

*Primary Adrenal Insufficiency*

Workup for primary adrenal insufficiency should include serum cortisol, as well as a comprehensive metabolic panel (CMP) and renin levels. Follow-up evaluation for abnormal findings should include ACTH, LH, FSH, and testosterone. Hallmarks of adrenal damage include low AM cortisol (<5) with ACTH above the reference range, with or without abnormal electrolytes and symptoms. Other abnormalities may include hypotension, orthostatic hypotension, low sodium, and high potassium.

Endocrinology should be consulted for these patients, with specialist evaluation prior to any surgery or procedure. Hold immunotherapy. If patients are hemodynamically unstable, inpatient care and high-dose/stress-dose corticosteroids are recommended. Patients with severe symptoms including hypotension may require additional fluids. It is important to initiate corticosteroid replacement prior to other hormone replacement to avoid adrenal crisis. Steroid replacement will include hydrocortisone or prednisone, plus mineralocorticoid replacement (fludrocortisone). Immunotherapy can be resumed once endocrine replacement therapy has been established.

Physiologic hormone replacement will likely be required indefinitely (typically life-long). The goal for physiologic steroid replacement is to identify the lowest steroid dose needed to prevent symptoms of adrenal insufficiency. Provide patient education regarding stress doses of hydrocortisone in case of infection, trauma, or other medical event. Patients should wear a medical alert bracelet.

*Hyperglycemia/Diabetes*

Fasting glucose is preferred to assess potential hyperglycemia. Note that high-dose corticosteroids can induce or exacerbate hyperglycemia. Consider endocrinology referral and appropriate management if patients are symptomatic or hyperglycemia remains persistently uncontrolled. Management is guided by patient history of type II diabetes mellitus (T2DM), glucose levels, and concern for diabetic ketoacidosis (DKA). Symptoms of 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.

For patients with new-onset hyperglycemia less than 200 mg/dL, and/or a history of T2DM with low suspicion for DKA, the observed hyperglycemia may be corticosteroid-related or due to preexisting diabetes. Immunotherapy can be continued with serial blood glucose monitoring at each dose. Diet and lifestyle modifications are recommended as needed along with medical therapy per institutional guidelines.

Further workup is warranted for findings of 1) new-onset hyperglycemia >200 mg/dL; 2) random blood glucose >250 mg/dL; or 3) history of T2DM with glucose levels >250 m/dL. If any of the previous findings are noted, consider new-onset type I diabetes mellitus (T1DM) and evaluate for DKA. ICI-related development of T1DM is rare (1%–2%) but can be life-threatening if insulin therapy is not provided. Management and monitoring should be directed by endocrinology team. DKA requires hospitalization and immunotherapy hold. Management of DKA varies by institution and may include (but is not limited to) IV fluids with or without potassium supplementation, IV insulin, and hourly testing of glucose, serum ketones, blood pH, and anion gap. Corticosteroid therapy is not recommended for treating T1DM as there is insufficient evidence to suggest that it effectively reverses ICI-related T1DM, and it may further complicate glycemic control.

***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.[217,218] 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%.[219,220] Observed rates for combination immunotherapy (PD-1/PD-L1 inhibitor plus anti-CTLA-4) are higher than for monotherapy with other ICIs.[217,218,221] 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.[217,221]

A 2016 meta-analysis of 20 clinical trials of PD-1 inhibitors that enrolled 4496 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.[218] 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 observed among the largest disease cohorts, melanoma and NSCLC, for both monotherapy and combination therapy. Of the patients diagnosed with pneumonitis in this study, most low-grade cases were treated in the outpatient setting, but 19% of patients with G2 pneumonitis and all patients ≥G3 required inpatient care. All mild pneumonitis (G1) cases were managed using ICI dose holds or oral corticosteroid, while all moderate and severe cases received oral or IV corticosteroid. Among patients with G3 or higher pneumonitis, 42% required additional immunosuppression with infliximab alone or infliximab with cyclophosphamide.[217]

NCCN Recommendations

These guidelines characterize mild pneumonitis (G1) as asymptomatic, confined to less than 25% of the lung parenchyma or a single lobe. Moderate pneumonitis (G2) is characterized by the presence of new or worsening symptoms including shortness of breath, cough, chest pain, and fever. Severe pneumonitis (G3) involves all lobes of the lung or

greater than 50% of the lung parenchyma. The symptoms typically limit self-care activities of daily living (ADLs). Life-threatening (G4) pneumonitis involves serious respiratory compromise.

Baseline pulmonary function should be determined by measuring oxygen saturation (at rest and with ambulation), and pulmonary function tests are recommended for high-risk patients. Repeat oxygen saturation tests as symptoms indicate and evaluate for pneumonitis via chest CT. Pneumonitis can present as focal or diffuse inflammation of the lung parenchyma and is typically identified on CT imaging as ground-glass opacities. For mild to moderate pneumonitis (G1), consider holding immunotherapy and obtain chest CT, with repeat imaging in 4 weeks or sooner if clinically indicated for worsening symptoms. For mild pneumonitis, reassess in 1 to 2 weeks, including physical exam and pulse oximetry at rest and with ambulation. For moderate pneumonitis (G2), consult pulmonology and order infectious workup to include nasal swab for potential viral pathogens as well as sputum, blood, and urine cultures. The panel recommends infectious evaluation with institutional immunocompromised panel. Bronchoscopy with bronchoalveolar lavage (BAL) can be used to rule out infection and malignant lung infiltration. Consider chest CT with repeat imaging in 3 to 4 weeks. Consider empiric antibiotics if infection has not yet been fully excluded and begin methylprednisone/prednisolone at 1–2 mg/kg/day. Monitor every 3 to 7 days with physical examination and pulse oximetry. Treat with corticosteroid until symptoms improve to ≤ G1 and then taper over 4 to 6 weeks. The panel recommends treating per the algorithm for severe (G3) pneumonitis if no improvement is seen after 48 to 72 hours of corticosteroid therapy.

Permanently discontinue immunotherapy for all cases of severe or life-threatening pneumonitis. Inpatient care is required. Complete infectious workup and bronchoscopy with BAL as per the G2 algorithm and consult with pulmonology and infectious disease specialists. Consider empiric antibiotics if infection has not yet been fully excluded and begin methylprednisone/prednisolone at 1–2 mg/kg/day. Assess response within 48 hours and plan a slow corticosteroid taper over ≥6 weeks. If no improvement is observed after 48 hours of treatment, consider additional immunosuppression with any of the following agents: infliximab, MMF, or IVIG.

Resumption of immunotherapy following mild pneumonitis can be considered upon radiographic evidence of improvement. Following G2 irAE, rechallenge can be considered upon resolution of pneumonitis to ≤ G1 and no requirement for steroid.

***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.[195,222] Based on a review of phase II and III clinical trials of ICIs enrolling 3695 patients, the incidence of high-grade renal toxicity was 0.6%.[222] However, reviews of emerging data suggest that incidence of renal toxicity could be considerably higher.[223,224] 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.[225]

In the largest case series to date, time to onset of renal toxicity was around 3 months from initiation of ICI therapy, but varied from 3 weeks to approximately 8 months.[222] Within the cohort of 13 patients, kidney injury was preceded by an extrarenal irAE in 7 patients and pyuria (>5 white blood cells [WBC] per high-power field [HPF]) 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 patients showed recovery of renal function (complete recovery in 2, partial recovery in 7). Four patients required hemodialysis, and 2 remained dialysis-dependent.[222] Other case reports/series have discussed similar

approaches to diagnosis and management of ICI-related nephritis.[226-228] Notably, there is conflicting evidence surrounding the efficacy of corticosteroid therapy for treating acute interstitial nephritis linked to non-ICI–related causes.[229,230]

NCCN Recommendations

Elevated serum creatinine could indicate a developing renal irAE. Signs of acute renal failure may include azotemia, creatinine elevation, and ability to maintain acid/base or electrolyte balance, and changes in urine output. Mild renal irAEs (G1) are categorized by serum creatinine levels 1.5 to 2 times above baseline or an increase in ≥0.3 mg/dL. Creatinine levels of 2 to 3 times above baseline are considered moderate renal irAEs (G2). With severe irAEs (G3), creatinine levels may be in excess of 3 times above baseline, or >4.0 mg/dL. Creatinine levels >6 times above baseline indicate life-threatening renal issues (G4) and necessitate dialysis.

Upon development of signs of acute renal damage, the panel recommends conducting a medication review and limiting/discontinuing any nephrotoxic medications (eg, NSAIDS). Dose adjust remaining medications to creatinine clearance. Evaluate for and rule out other potential alternative etiologies for abnormal findings, testing as indicated for potential prerenal and postrenal causes (eg, contrast-enhanced imaging). Distinguish cell infiltrate from immune-complex–mediated injury. Possible considerations should include cardiomyopathy, heart failure, pulmonary hypertension, kidney stones/obstruction, hypovolemia due to a primary GI issue, diuretics, and infection. Protein-to-creatinine ratio in spot urine samples can be used to assess proteinuria, with follow-up testing for findings of proteinuria above 3 g/24-hour (ie, ANA, RF, ANCA, anti-dsDNA, serum C3 and C4, CH50).

For mild to moderate renal irAEs (G1), follow creatinine and urine protein every 3 to 7 days. Consider holding immunotherapy for G1 renal dysfunction, and hold immunotherapy dose in the setting of moderate renal irAEs (G2). If other causes are ruled out, administer prednisone 0.5–1 mg/kg/day. Increase dose to 1–2 mg/kg/day of methylprednisone/prednisolone for persistent G2 issues beyond 1 week. After G1/2 irAEs, once symptoms resolve to ≤ G1, consider resuming immunotherapy concomitant with corticosteroid.

Permanently discontinue immunotherapy if severe/life-threatening renal irAEs occur. Consider inpatient care, consult nephrology and consider renal biopsy, and initiate methylprednisone/prednisolone at 1–2 mg/kg/day. For persistent findings above G2 after 1 week of steroid therapy, consider adding one of the following agents: azathioprine, monthly cyclophosphamide, cyclosporine, infliximab, or mycophenolate.

When corticosteroid therapy is used to manage renal irAEs, continue until improvement to ≤ G1, then taper over 4 to 6 weeks.

***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 neuropathy.[231-233] Dry eye and uveitis have been the most commonly reported ocular ICI-associated events, with a reported incidence between 1% and 24%.[233-235] 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.[232,233,236,237] Close cooperation with ophthalmologic specialists is critical for prompt diagnosis and optimal treatment.[232,235]

NCCN Recommendations

Signs or symptoms such as blurred/distorted vision, changes in color

vision, blind spots, photophobia, eye pain, eyelid swelling, and proptosis may indicate the development of an ocular irAE such as uveitis, episcleritis, or blepharitis. Episcleritis can be associated with red/purple discoloration of the eye, and uveitis may present with eye redness. Grading for uveitis is broken out by mild uveitis (G1), anterior uveitis (G2), posterior or panuveitis (G3), and uveitis causing vision of 20/200 or worse (G4). Episcleritis is graded as mild (G1), associated with vision of 20/40 or better (G2), associated with vision of 20/40 or worse (G3), or associated with vision of 20/200 or worse (G4).

For mild uveitis, episcleritis, or blepharitis, continue immunotherapy, provide artificial tears, and refer to ophthalmology. Avoid eye irritants such as contact lenses and cosmetics. Hold immunotherapy for G2 ocular irAEs and seek urgent ophthalmology consultation. Permanently discontinue immunotherapy for any G3 or G4 ocular irAEs and obtain emergent ophthalmology consultation. Treatment for moderate to severe irAEs should be guided by ophthalmology and will likely include ophthalmic and systemic prednisone/methylprednisone. For ophthalmic conditions refractory to high-dose systemic corticosteroid, consider adding infliximab or an antimetabolic agent (eg, methotrexate).

Corticosteroid treatment should be continued until resolution to ≤ G1, followed by dose taper over 4 to 6 weeks. For G2 ocular irAEs, the panel suggests consideration of resuming immunotherapy in consultation with ophthalmology upon resolution of the irAE to ≤ G1. Rechallenge is contraindicated after high-grade irAEs.

***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 quite challenging to diagnose due to nonspecific symptoms, variability in presentation, and the wide range of differential diagnoses to consider.[144,146,238] 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.[144,145,238-242] The neurologic irAEs that most commonly resulted in fatality were encephalitis and myasthenia gravis.[91]

A systematic review of the literature examined data on neurologic AEs from case reports and prospective ICI trials (59 trials, n = 9208).[243] 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.[243] Generally, reviews report a ≤1% incidence of high-grade neurologic irAEs across various ICI regimens.[146,241,243] 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 = 3763).[146] Out of 3763 patients, 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.[144,146,243] Corticosteroid therapy is usually employed as the first line of treatment for neurologic irAEs; high-dose IV corticosteroids and ICI discontinuation was employed in the setting of higher-grade events.[144,146] Prompt treatment is critical for reducing long-term morbidity and mortality.[113,144,146,238,241] Median time to irAE resolution

has been reported at just under 8 weeks.[146] Of note, unlike canonical cases of GBS, ICI-mediated development of GBS-like syndrome has been successfully managed using corticosteroid therapy.[243]

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.[144,146,240] 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 MMF).[144,145] At present, there are no definitive outcomes data 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).[144]

NCCN Recommendations

*Myasthenia Gravis*

If myasthenia gravis is suspected, obtain neurology consultation. Assessment should include pulmonary function testing, electromyography (EMG) and nerve conduction study, as well as consideration of brain and/or spine MRI if symptoms are suggestive of malignant CNS involvement. Laboratory testing should include acetylcholine receptor and muscle-specific tyrosine kinase antibodies, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), creatinine phosphokinase, and aldolase for possible superimposed myositis. If the patient has respiratory insufficiency or elevated CPK, perform cardiac examination to include ECG, troponin, and transthoracic echocardiogram for possible concomitant myocarditis.

Hold immunotherapy for moderate symptoms (G2) with some interference in ADLs. Administer pyridostigmine and gradually increase to a maximum of 120 mg orally four times/day as tolerated and based on symptoms. Consider low-dose oral prednisone at 20 mg daily and gradually increase to a target dose of 1 mg/kg/day (not to exceed 100 mg daily). Taper these agents based on symptom improvement. Consider resuming immunotherapy based on steroid responsiveness. Severe cases (G3/4) warrant permanent discontinuation of immunotherapy, hospitalization, and neurology consultation with daily neurologic evaluation and frequent pulmonary function testing. Start methylprednisolone 1–2 mg/kg/day. For patients with refractory, severe, or worsening symptoms, initiate plasmapheresis or IVIG. Medications that can worsen this condition, such as beta-blockers, ciprofloxacin, and IV magnesium, should be avoided.

*Guillain-Barré Syndrome (GBS)*

Inpatient care with access to intensive care–level monitoring is recommended; consult neurology. Recommended testing includes spinal MRI, lumbar puncture, serum antibody testing for GBS variants, and pulmonary function testing. Permanently discontinue immunotherapy for all cases of GBS and provide inpatient care with capability for rapid transfer to ICU-level monitoring. Initiate IVIG or plasmapheresis in addition to pulse dose methylprednisolone (1 g/d for 5 days). Conduct frequent neurologic examinations and pulmonary function testing. Monitor for concurrent autonomic dysfunction and provide non-opioid analgesic for management of neuropathic pain.

Unlike classical GBS, in immune-mediated GBS, cerebrospinal fluid (CSF) findings often include elevated protein and WBC count. Although corticosteroid is not typically indicated in idiopathic GBS, a trial is reasonable if the suspected cause is ICI therapy. Slow steroid taper is recommended once symptoms resolve. Immunotherapy rechallenge is not recommended.

*Peripheral Neuropathy*

Evaluate for other potential causes when assessing mild to moderate peripheral neuropathy. Potential factors include medication, infection, metabolic or endocrine disorders, vascular or autoimmune disease, and trauma, among other potential causes. Any cranial nerve involvement should be treated as a G2 irAE. Gastrointestinal tract paresis due to myenteric neuritis is a rare toxicity associated with ICI therapy.[244] The presentation may be fulminant with profound ileus. Early institution of high-dose steroids in concert with multidisciplinary management is recommended.

In the setting of peripheral neuropathy, obtain neuraxial imaging as recommended by neurology. For mild cases, consider holding immunotherapy and continue to monitor symptoms for any new interference with ADLs due to pain, weakness, difficulty walking, ataxia, or autonomic changes. Hold immunotherapy for moderate cases (G2) and observe closely. If symptoms progress, initiate methylprednisolone/prednisone at 0.5–1 mg/kg/day and administer gabapentin, pregabalin, or duloxetine for pain. Increase dose to 2 to 4 mg/kg/day if further progression. Severe peripheral neuropathy (G3/4) is not necessarily GBS, but management can be similar. Gabapentin, pregabalin, or duloxetine can be administered for neuropathic pain.

*Aseptic Meningitis*

When assessing immunotherapy patients for meningitis, exclude potential infectious causes and consider neurology consultation. The panel recommends brain MRI (with and without contrast) to include the pituitary gland. ACTH and AM cortisol can be used to rule out adrenal insufficiency. Lumbar puncture may be helpful in making a differential diagnosis. Relevant measures include opening pressure, CSF cell counts, protein glucose, gram stain, and culture for infectious organisms. Findings may include elevated WBC count with normal glucose, culture, and gram stain. Reactive lymphocytes or histiocytes may be observed on cytology. Based on these results, conduct polymerase chain reaction (PCR) for herpes simplex virus or other suspected viral infections.

If severity is mild to moderate, hold immunotherapy. If severe (G3/4), provide inpatient care and permanently discontinue immunotherapy. IV acyclovir can be considered until PCR results are obtained. Once infectious etiology has been ruled out, closely monitor or initiate corticosteroid therapy at 0.5–1 mg/kg/day. Provide methylprednisolone dose of 1–2 mg/kg/day for moderate to severe symptoms. Taper corticosteroid rapidly once symptoms resolve. Consider resuming immunotherapy following mild to moderate aseptic meningitis only if symptoms have completely resolved.

*Encephalitis*

Infectious causes of encephalitis should be excluded. Consult neurology and perform brain MRI (with and without contrast), lumbar puncture, and electroencephalography (EEG) to rule out seizure activity. Laboratory testing should include CMP, complete blood count (CBC), thyroid panel including thyroid peroxidase (TPO) and thyroglobulin, as well as autoimmune and paraneoplastic panels. Also test ESR, CRP, and antineutrophil cytoplasmic antibody if vasculitis process is suspected. MRI may reveal T2/FLAIR changes typical of what is seen in autoimmune encephalopathies or limbic encephalitis. CSF may have elevated WBCs with lymphocytic predominance and/or elevated protein.

Hold immunotherapy for mild cases (G1), but permanently discontinue if moderate or severe (G2/3/4) encephalitis occurs. Severe encephalitis warrants inpatient care. A trial of acyclovir can be initiated until CSF PCR results are obtained. Also consider a trial of methylprednisolone 1–2 mg/kg/day. If symptoms are severe/progressive, or if oligoclonal bands are present on CSF, consider pulse-dose corticosteroid (1 g/day for 3–5 days) in addition to IVIG. Consider rituximab if limited or no improvement is seen

after 1 to 2 weeks and test results are indicative of autoimmune encephalopathy.

*Transverse Myelitis*

Consult with neurology. Recommended assessment includes MRI of the brain and spine, lumbar puncture, and evaluation for urinary retention or constipation. Examine CSF for cell counts, protein, glucose, oligoclonal bands, cytology, and onconeural antibodies, and conduct viral PCRs as indicated. Laboratory studies include $B_{12}$ levels, HIV testing, rapid plasma reagin (RPR), ANA, anti-Ro/La antibodies, TSH, and aquaporin-4 IgG and paraneoplastic panel. Inpatient care is recommended. Discontinue immunotherapy. Provide pulse-dose methylprednisolone (1 g/day for 3–5 days) and strongly consider IVIG or plasmapheresis.

***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.[67,245,246] Efforts to characterize cardiac irAEs associated with ICI therapy have begun to provide a better understanding of ICI-associated myocarditis. Data collected over 4 years from 8 sites revealed 35 cases of ICI-mediated myocarditis, which were compared to a sample of patients on ICI therapy without myocarditis.[246] 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.[91,246-248]

Recent analysis of the WHO database revealed 101 individual case safety reports of severe myocarditis following initiation of ICI therapy.[248] 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%. Data on cardiovascular comorbidities were not available, but only 25% were on a cardiovascular or diabetes medication regimen.[248]

Based on multicenter registry data, myocarditis was observed more often in patients receiving combination ICI therapy and in patients with diabetes.[246] 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.”[246] Troponin levels of ≥1.5 ng/mL were associated with a 4-fold increased risk of MACE (HR, 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.[246]

Pre-existing cardiovascular pathology was identified in the majority of patients (5/8) in one case series.[245] Co-occurrence with non-cardiac irAEs was also observed in over 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.[245] 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.[91] Case reports of ICI-related myocarditis have reported irAE flare during steroid taper or ICI rechallenge.[249,250] IVIG was successfully used in a case report of smoldering ICI-related myocarditis that initially responded to corticosteroid but flared upon taper.[249]

NCCN Recommendations

Immediate cardiology consultation and inpatient care is recommended. Assessment should include telemetry monitoring, ECG, and cardiac MRI. Recommended laboratory testing includes cardiac biomarkers (creatine kinase and troponin) and inflammatory biomarkers (ESR, CRP, and WBC count). Seek to rule out other potential causes via viral titers, echocardiogram, or biopsy in the case of severe symptoms.

In the setting of severe (G3) cardiac irAE, arrhythmia may be accompanied by significant echocardiogram findings without hypotension, and cardiac biomarkers above the ULN. Life-threatening (G4) cardiac irAEs are denoted by arrhythmia, hemodynamic instability, and cardiac biomarkers more than 3 times the ULN. Permanently discontinue immunotherapy for any G3 or G4 cardiovascular irAEs. The panel recommends methylprednisolone pulse dosing (1 g/day for 3–5 days). Treat until cardiac function returns to baseline, then dose taper over 4 to 6 weeks. For life-threatening cases (G4), if no improvement is noted within 24 hours, consider adding infliximab or anti-thymocyte globulin (ATG).

***Musculoskeletal Toxicity***

Musculoskeletal and rheumatic irAEs include 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.[251]

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.[251] 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%.[112,251-253]

Among a prospective cohort study of 524 patients receiving ICIs, 35 (6.6%) were referred to rheumatology.[112] 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.[254] 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 their findings on the distinct clinical presentation of IA within a cumulative series of 30 patients who received various ICI regimens.[255] 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 CRP, 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).[255]

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.[112,255,256]

NCCN Recommendations

*Inflammatory Arthritis (IA)*

When assessing for IA, note the number of joints involved, perform a functional assessment, and obtain imaging as appropriate (eg, x-ray, joint ultrasound, joint MRI). Continue immunotherapy if arthritis is mild and administer NSAIDS or low-dose corticosteroid for refractory symptoms. Intraarticular steroids can be considered depending on joint location and the number of involved joints. For moderately severe arthritis, consider holding immunotherapy and administer prednisone 0.5 mg/kg/day for 4 to 6 weeks. If no improvement is seen within a month, treat per the algorithm for severe IA and seek rheumatology consultation. For severe arthritis that limits instrumental ADLs (with or without irreversible joint damage), hold immunotherapy and prescribe methylprednisolone/prednisone 1 mg/kg/day. If no improvement by week 2, consult rheumatology for consideration of additional disease modifying anti-rheumatic drugs depending on the clinical phenotype of inflammatory arthritis. Consider the co-existence of other irAEs in which choice of immunosuppression may be relevant; options may include infliximab, methotrexate, tocilizumab, sulfasalazine, azathioprine, leflunomide, and IVIG. Continued lack of improvement warrants rheumatology consultation for consideration of additional disease-modifying anti-rheumatic agents such as sulfasalazine, methotrexate, or leflunomide.

Continue to treat IA with corticosteroid until symptoms improve to a mild level, then taper the dose over 4 to 6 weeks. Perform serial rheumatologic examinations to monitor the patient's condition; if levels were initially elevated, ESR and CRP testing can also be used to monitor treatment response. After an immunotherapy hold, clinicians can consider resuming therapy upon stabilization or adequate management of symptoms. However, severe IA that impairs ADLs and quality of life may require permanent discontinuation of immunotherapy.

*Myositis/Myalgia (Muscle Weakness)*

Order a CMP and check creatine kinase and aldolase levels during workup for myositis or myalgia. Immunotherapy can continue uninterrupted in the setting of mild pain. Continue serial creatine kinase/aldolase monitoring and treat pain as indicated. For moderate, severe, or life-threatening (ie, myositis only, urgent intervention required) irAEs, obtain muscle MRI and EMG. Administer prednisone 1–2 mg/kg/day and treat pain as appropriate. Hold immunotherapy if creatine kinase/aldolase levels are elevated. Muscle biopsy can be considered for severe or refractory cases. Creatine kinase/aldolase serial monitoring should continue until symptoms resolve or corticosteroid has been discontinued. Corticosteroid treatment should continue until symptoms are ≤ G1, followed by dose taper over 4 to 6 weeks. Consult rheumatology for follow-up as well as neurology for myositis.

## CAR T-Cell Therapy

*Section under development.*

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