National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Management of Immunotherapy-Related Toxicities

Version 1.2024 — December 7, 2023

NCCN.org

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Management of Immunotherapy-Related Toxicities

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NCCN Guidelines Panel Disclosures

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λ Cardio-oncology
ϖ Dermatology
ð Endocrinology
¤ Gastroenterology
‡ Hematology/Hematology oncology
Þ Internal medicine
† Medical oncology
∩ Nephrology
Ψ Neurology/Neuro-oncology
Nursing
۞ Ophthalmology
Σ Pharmacology
Ξ Pulmonary medicine
& Rheumatology
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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.

Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

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

See NCCN Categories of Evidence and Consensus.

Terminologies in all NCCN Guidelines are being actively modified to advance the goals of equity, inclusion, and representation.

Updates in Version 1.2024 of the NCCN Guidelines for Management of Immunotherapy-Related Toxicities from Version 3.2023 include:

Global Changes

• References updated throughout the Guidelines

Management of Immune Checkpoint Inhibitor-Related Toxicities

IMMUNO-1

• Footnote a modified: Prior to initiating treatment, counsel patients and caregivers on the warning signs and symptoms of immune-related adverse events (irAEs). Principles of Immunotherapy Patient Education (IMMUNO-B). ~~For disease-specific COVID-19 recommendations, see the NCCN COVID-19 Resource page.~~ *For guidance on general recommendations for vaccination in patients with cancer, see NCCN Guidelines for the Prevention and Treatment of Cancer-Related Infections*. (Also for IMMUNO-2)

IMMUNO-3

• Conditions, CARDIO Myocarditis modified: Chest pain, shortness of breath, fatigue, ~~irregular heart beat~~ *palpitations* (arrhythmia: *heart block or ventricular ectopic beats*), syncope, generalized weakness. *This adverse event may occur in conjunction with myositis and/or myasthenia gravis; these entities must be ruled out.*

• Conditions, DERM Lichen planus modified: Violaceous (dark red/purple) *papules and* plaques without scale over the trunk and extremities, significant pruritus.

• Conditions, ENDO Subclinical hypothyroidism removed.

• Conditions, ENDO modified: ~~Clinical (~~Overt~~) primary~~ hypothyroidism.

IMMUNO-4

• New ENDO Central hypothyroidism row added.

• New GI Cholestasis row added.

• Conditions, MUSCULO modified: Polymyalgia rheumatica (PMR) ~~and giant cell arteritis (GCA)~~: PMR symptoms: fatigue and/or muscle and joint pain typically in shoulders and hips ~~GCA symptoms: visual symptoms, headache, scalp tenderness, jaw claudication~~

• New MUSCULO Giant cell arteritis (GCA) row added.

IMMUNO-5

• New NEURO ADEM [acute demyelinating encephalomyelitis] row added.

• NEURO: Demyelinating disease row removed.

• New NEURO Optic neuritis row added.

• New NEURO Transverse myelitis row added.

Infusion-Related Reactions

ICI_INF-1

• Footnote a modified: Symptoms include: Fever/chills/rigors, *back pain,* urticaria/pruritus, angioedema...

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Cardiovascular Adverse Event(s)

ICI_CARDIO-1

- Assessment/Grading
  - 7th bullet modified: Cardiac MRI *with and without contrast* (if possible)
  - 8th bullet modified: Consider cardiac catheterization and/or myocardial biopsy *as clinically indicated* ~~in a specialized center if myocarditis is suspected~~
  - 9th bullet modified: Consider viral titers ~~(especially COVID-19)~~
- Management
  - Myocarditis
    - ◊ 4th bullet modified: If no improvement within 24–48 hours on steroids, *initiate additional immunosuppression* ~~consider further interventions~~ *(listed in alphabetical order)*:
      - Mycophenolate sub bullet moved from 4th to 7th sub bullet.
      - New 6th sub bullet added: Methotrexate.
    - ◊ New 5th bullet added: Abatacept with ruxolitinib has been used in concomitant myositis and myocarditis.(Also for ICI_MS-2)

ICI_CARDIO-1A

- Footnote a modified: Myocarditis symptoms are nonspecific and may occur as early as days to weeks after 1–2 doses of ICI. Although rare, myocarditis is often severe and associated with myositis/myasthenia gravis (3 M's), and more common with combination therapy. In *most* fatal cases, conduction abnormalities were the cause of death, and ejection fraction was preserved.
- Footnote i modified: Perform a *TB blood test (eg,* T-Spot*/QuantiFERON* ~~and quantiFERON~~ tuberculosis [TB] gold*)* (depending on facility) and ~~consider~~ hepatitis testing at time of suspected toxicity to facilitate administration.
- New footnote m added: Salem et al. Cancer Discov. 2023;13:1100-1115. (Also for ICI_MS-2)

Dermatologic Adverse Event(s)

ICI_DERM-1

- Management
  - Mild (G1), 3rd bullet modified: *Consider trial of* oral antihistamine for *symptomatic relief of* pruritus. (Also for Moderate [G2])
  - Moderate (G2), new bullet added: Consider dermatology consultation.
  - Severe modified: (G3~~-4~~)
    - ◊ 3rd bullet modified: Prednisone*/IV methylprednisolone* 0.5–1 mg/kg/day (increase dose up to 2 mg/kg/day if no improvement)
- New footnote g added: Topical steroids by potency: High (eg, clobetasol 0.05% or fluocinonide 0.05% [cream or ointment]); Moderate (eg, triamcinolone 0.1% [cream, ointment, lotion] or betamethasone valerate [lotion]). (Also for ICI_DERM-2, ICI_DERM-3A, ICI_DERM-4, ICI_DERM-5)

ICI_DERM-2

- This page has been significantly revised.

ICI_DERM-3

- Bullous Dermatitis, Management
  - Moderate (G2)
    - ◊ 3rd bullet modified: If no improvement after 3 days, consider adding rituximab *or dupilumab.*
  - Severe (G3) OR Life-threatening (G4)
    - ◊ 3rd bullet modified: Consider IVIG (1 g/kg/day x 2 days with monthly cycle until clear) as an adjunct to rituximab *or dupilumab* ~~(1 g/kg/day x 2 days with monthly cycle until clear)~~

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Updates in Version 1.2024 of the NCCN Guidelines for Management of Immunotherapy-Related Toxicities from Version 3.2023 include:

ICI_DERM-3A

- Footnote p modified: Skin biopsies ~~may also~~ *should* be performed on ~~peripheral bullae~~ *perilesional* intact skin. Two biopsies should be performed with one being sent for direct immunofluorescence testing *in Michel's media, if available, or* in normal saline *(if Michel's media not available*).
- New footnote w added: Shipman W, et al. Br J Dermatol. 2023;189:339-341.

ICI_DERM-4

- Management
  - Mild <10% BSA
    - ◊ New 2nd bullet added: High potency topical steroid or Tacrolimus 0.1% ointment. (Also for Severe >30% BSA)
  - Moderate: 10%–30% BSA or not responsive to high-potency topical steroids
    - ◊ 2nd bullet modified: High potency topical steroid *or Tacrolimus 0.1% ointment.*
    - ◊ 5th bullet modified: *Narrow-band UVB* phototherapy, if available and feasible. (Also for ICI_DERM-5)
  - Severe: >30% BSA, 4th bullet: new 1st sub bullet added: Referral to dermatology.
- Footnote z modified: Violaceous (dark red/purple) *papules and* plaques without scale over the trunk and extremities, significant pruritus. Erosions and striae (white lines intersecting) in the oral and vulvar mucosa.
- Footnote cc modified: ~~Methotrexate,~~ Azathioprine, cyclosporine, *hydroxychloroquine, methotrexate and mycophenolate mofetil.*

ICI_DERM-5

- Management
  - Moderate: 10%–30% BSA or not responsive to high-potency topical steroids
    - ◊ New 6th bullet added: Refer to dermatology for consideration of approved biologics.

ICI_DERM-6

- This page has been extensively revised.

ICI_DERM-6A

- New footnote added: Avoid crunchy, spicy, acidic, or hot food/drink as appropriate for comfort.
- Footnote removed: Practical management to include dietary consideration and oral care management (such as avoidance of acidic food and drink).
- Footnote ii modified: To ensure adequate hygiene and protect against the risk of dental caries; *consider if mild and strongly consider if moderate or severe inflammation.*
- Footnote jj modified: Assist~~ance~~ in the management of persistent mucositis or if oropharynx/larynx involved; *consider if mild or strongly consider if moderate or severe* (especially if airway ~~concern~~ *involved*).
- Footnote ll modified: Eg, Liquid dexamethasone *0.5 mg/5ml elixir* or fluocinonide 0.05% gel.
- Footnote nn modified: Eg, Clobetasol 0.05% ~~(~~gel ~~or compounded solution preferred)~~, compounded budesonide 3 mg/10 mL solution.

ICI_DERM-7

- Dry mouth (Sicca syndrome), Management
  - Mild (G1):
    - ◊ New 2nd bullet added: Dietary modifications [Also for Moderate (G2)/ severe (G3)]
    - ◊ 4th bullet modified: Topical measures *(water sips, saliva substitutes, and moisture-preserving mouth rinses, toothpaste, or spray)*
    - ◊ New 5th bullet added: Salivary stimulants (sugarless chewing gum, lozenges, or candy)
  - Moderate (G2)/ severe (G3), 5th bullet modified: Systemic sialagogues (*cevimeline or* pilocarpine ~~or cevimeline~~)

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Updates in Version 1.2024 of the NCCN Guidelines for Management of Immunotherapy-Related Toxicities from Version 3.2023 include:

ICI_DERM-7A

- Footnote removed: Increase water intake; oral moisturizers; sugarless chewing gum, lozenges, or candy and/or moisture-preserving dental products (toothpaste, mouthwash, and spray).

Endocrine Adverse Event(s)

ICI ENDO-1

- Management
  - DKA present
    - 1st bullet modified: *Urgent* endocrine consultation
    - 5th bullet modified: Initiate insulin, as directed by inpatient team or endocrinologist, *and close glucose monitoring (consider early use of continuous glucose monitoring [CGM])*
  - DKA not present:
    - 1st bullet modified: *Urgent* endocrine consultation, *consider inpatient care* ~~if possible~~
    - 2nd bullet modified: Initiate insulin *and close glucose monitoring consistent with T1DM*, as directed by ~~inpatient team or~~ endocrinologist
- Footnote f modified: The development of ICI-T~~1~~*1*DM can be life-threatening if insulin therapy is not provided. Once new type ~~1~~*1* DM is diagnosed, management and monitoring should be directed by endocrinology team. ICI-T~~1~~*1*DM may be permanent. Autoantibodies are not required for diagnosis. *Empiric treatment as T1DM recommended if c-peptide unknown.*

ICI ENDO-2

- This page has been extensively revised.

ICI ENDO-3

- Management
  - 3rd bullet
    - 1st sub bullet modified: If resolved, no further therapy for thyrotoxicosis. Thyrotoxicosis often evolves to hypothyroidism (50%–90%) requiring treatment with thyroid hormone replacement (see *Overt hypothyroidism* ~~Clinical, primary hypothyroidism~~ on ICI_ENDO-2 for levothyroxine dosing).

ICI_ENDO-4

- This page has been extensively revised.

ICI_ENDO-4A

- This page has been extensively revised.

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Updates in Version 1.2024 of the NCCN Guidelines for Management of Immunotherapy-Related Toxicities from Version 3.2023 include:

Fatigue

ICI_FTG-1

- Assessment/Grading
  - 2nd bullet
    - ◊ New 7th sub-bullet added: CK and cardiac enzymes
  - New 4th bullet added: Assess for depression (consider PHQ-9)
- Management
  - Moderate (G2)
    - ◊ 1st bullet modified: Continue immunotherapy if impact on ADLs can be mitigated by active management; ~~Consider a pause~~ *otherwise hold* immunotherapy to assess for improvement in fatigue
- Follow-up
  - Severe (G3-4)
    - ◊ New 3rd bullet added: Consider follow-up in 5–7 days (by phone or visit)

Gastrointestinal Toxicity

ICI_GI-1

- Management, Mild (G1)
  - 2nd bullet
    - ◊ New 2nd sub bullet added: Caution is warranted to avoid masking symptoms; discontinue antidiarrheals if diarrhea persists, to assess response to immunosuppressive therapy.

ICI_GI-2

- Footnote q modified: An FDA-approved biosimilar *for infliximab or ustekinumab* is an appropriate substitute ~~for infliximab~~. (Also for ICI_GI-3)
- Footnote r modified: Perform infectious disease screening (HIV; hepatitis A, B, C) and *TB blood test (eg,* T-Spot/QuantiFERON TB gold) (depending on facility), ... (Also for ICI_GI-3)
- New footnote t added: Zou F et al. J Immunother Cancer 2021;9:e003277 (Also for ICI_GI-3)
- Footnote u modified: Esfahani K, et al. N Engl J Med 2020;382;2374-2375; Thomas A, et al. N Engl J Med 2021;384:581-583; Bishu S, et al. Gastroenterology 2021;160:932-934; *Shirwaikar et al. Am J Gastroenterol.2023;118(9):1679-1683* (Also for ICI_GI-3)

ICI_GI-3

- Management
  - 2nd bullet modified: G4: ~~Permanently~~ Discontinue immunotherapy agent responsible for toxicity.
  - 4th bullet, 1st sub bullet modified: *If* no response in 1–2 days *or unable to transition to oral steroids, additional immunosuppression required.* Continue steroids and strongly consider adding infliximab or vedolizumab

ICI_GI-4

- This page has been extensively revised.

ICI_GI-5

- This page has been extensively revised.

ICI_GI-5A

- This page has been extensively revised.

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Updates in Version 1.2024 of the NCCN Guidelines for Management of Immunotherapy-Related Toxicities from Version 3.2023 include:

ICI_GI-6
- New algorithm/page for elevated alkaline phosphatase (predominant) with or without bilirubin/AST/ALT elevation

ICI_GI-6A
- New page of footnotes for elevated alkaline phosphatase (predominant) with or without bilirubin/AST/ALT elevation

Musculoskeletal Toxicity

ICI_MS-1
- This page has been extensively revised.

ICI_MS-1A
- Footnote l modified: If improving after 2-4 weeks, begin prednisone taper by 5 mg/week. ~~If unable to taper, or no response, add csDMARD.~~
- Footnote r modified: TNF inhibitors include etanercept, adalimumab, infliximab, golimumab or certolizumab (FDA approved biosimilars as appropriate). *There is a slight increased risk of relapse.*
- Footnote s modified: Due to an increased risk of GI perforation with *IL-6 inhibitors* (tocilizumab *or sarilumab*), screen for diverticular disease prior to initiating therapy and ~~avoid~~ *use with caution* in patients with ~~a history of~~ *clinically active* diverticular disease.
- New footnote t added: An FDA-approved biosimilar is an appropriate substitute for tocilizumab.
- Footnote u modified: Consider ESR *and* CRP to monitor response if elevated at the onset of therapy. *Inflammatory arthritis may become a chronic process requiring long-term management*

ICI_MS-2
- Assessment/Grading
  - 3rd bullet modified: Creatine kinase (CK), aldolase, and troponin I or T levels, CMP (AST/ALT may be elevated in myositis), *ECG (compare to baseline if possible)*
  - 5th bullet modified: Consider MRI *without contrast*, EMG, muscle biopsy and myositis antibodies if clinically indicated.
- Management
  - Mild or Moderate
    - ◊ 4th bullet modified: If no response to therapy, consider re-evaluating for myasthenia gravis *(ICI_NEURO-1)* and myocarditis *(ICI_CARDIO-1)*, and escalate to management for severe or life-threatening myositis.
- Footnote ee modified: There have been case reports of a life-threatening triad of myositis, myocarditis, and myasthenia gravis. ~~See ICI_NEURO-1 and ICI_CARDIO-1 for assessment/grading and management.~~

ICI_MS-3
- This page has been extensively revised.

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Updates in Version 1.2024 of the NCCN Guidelines for Management of Immunotherapy-Related Toxicities from Version 3.2023 include:

Nervous System Toxicity

ICI_NEURO-1

- Assessment/Grading
  - 2nd bullet modified: Acetylcholine receptor (AChR) antibodies, anti–muscle-specific tyrosine kinase antibodies, *and anti-striational antibodies* in blood (not needed for diagnosis).
  - 4th bullet modified: *To rule out myositis/overlap syndrome, check* CPK *and* aldolase. ~~(to rule out myositis), and anti-striational antibodies~~
  - 6th bullet modified: EMG ~~with repetitive stimulation and~~ /nerve conduction study (NCS) *with repetitive nerve stimulation and, if available, single fiber EMG.*
  - 7th bullet modified: Consider MRI of the brain *with and without contrast* to rule out metastasis/leptomeningeal disease if there is facial/ocular/bulbar weakness
- Management
  - Moderate (G2) arm
    - ◊ 1st bullet modified: ~~Permanently~~ Discontinue immunotherapy
    - ◊ 3rd bullet, 1st sub bullet modified: *If no symptom improvement on low dose*
      - – Increase every 3–5 days to a target dose of 1 mg/kg/day but not more than 100 mg daily
      - – *Taper* steroid ~~taper~~ based on symptom improvement

ICI NEURO-2

- Assessment/Grading
  - 6th bullet modified: ~~Early~~ EMG/NCS
- Management
  - 1st bullet modified: ~~Permanently~~ Discontinue immunotherapy.

ICI_NEURO-4

- Assessment
  - Aseptic meningitis
    - ◊ New 2nd bullet added: Consider MRI of the spine with and without contrast, especially if abnormal neurologic exam of extremities, or unable to obtain exam (Also for encephalitis)
    - ◊ 3rd bullet modified: Lumbar puncture ~~if feasible~~
- Management
  - Aseptic meningitis
    - ◊ 2nd bullet modified: Consider ~~permanently~~ discontinuing immunotherapy if severe
  - Encephalitis
    - ◊ 2nd bullet modified: ~~Permanently~~ Discontinue immunotherapy if moderate/severe
- New footnote added: May reveal leptomeningeal enhancement that can resemble leptomeningeal metastasis. CSF sampling for cytology evaluation is needed to differentiate.

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ICI_NEURO-5

- Assessment
  - 4th bullet modified: B12, copper, HIV, *syphilis serologies,* ~~rapid plasma reagin (RPR),~~ ANA, anti-Ro/La antibodies, aquaporin-4 IgG, myelin oligodendrocyte glycoprotein (MOG) IgG, *autoimmune encephalopathy panel and* paraneoplastic panel
- Management
  - 1st bullet modified: ~~Permanently~~ Discontinue immunotherapy
  - 4th bullet modified: *If there is no response or worsening after 48 hours on high-dose IV methylprednisolone*, ~~Strongly~~ consider IVIG or plasmapheresis
- New footnote ff added: Vision loss, eye pain, decreased visual acuity, visual field loss, dyschromatopsia, relative afferent pupillary defect, optic disc edema
- Footnote gg modified: Acute or subacute weakness or sensory changes bilaterally, often with bowel/bladder changes and spinal level to pinprick, *hyperreflexia, positive Babinski.*
- New footnote hh added: May present with headache, confusion, seizures, depressed level of consciousness, speech abnormality, focal weakness, sensory change (numbness or tingling), ataxia/loss of balance, or vision loss.
- New footnote ii added: In patients with suspected optic neuritis, MRI of the orbits with and without contrast is recommended.

ICI_OCUL-1

- Assessment/grading
  - 1st bullet
    - 5th sub bullet modified: *Dilated* fundoscopic examination
    - New 6th sub bullet added: Slit lamp examination
  - Episcleritis
    - 2nd bullet modified: *Moderate decrease (worse than 20/20 but better than* 20/40, *or ≤3 lines decreased* vision ~~*or better*~~ *from baseline* (G2)
    - 3rd bullet modified: *Marked decrease* (worse than 20/40 *or >3 lines of decreased vision from baseline, up to 20/200)* (G3)
    - 4th bullet modified: 20/200 *or worse* vision (G4)
- New footnote b added: See ICI_MS-3 for management of Giant cell arteritis (GCA).

ICI_OCUL-2

- New additional algorithm for vision changes

ICI_PULM-1

- Management
  - Moderate (G2)
    - 3rd bullet, 2nd sub bullet modified: ~~Consider~~ Chest CT with contrast and repeat chest CT in 3–4 weeks
    - 4th bullet, 1st sub bullet modified: Consider bronchoscopy with BAL (send for institutional immunocompromised panel) and consider transbronchial lung biopsy if clinically feasible *to rule out progressive malignancy or fungal infections*
- New footnote n added: In people with pre-existing/underlying lung compromise, greater clinical suspicion and caution should be taken.

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ICI_PULM-2
- Management
  - Severe (G3-4) pneumonitis
    - 1st bullet modified: ~~Permanently~~ Discontinue immunotherapy.
- Foonote r modified: Mycophenolate mofetil is unlikely to improve steroid-~~refractory~~ *unresponsive* pneumonitis immediately but may have a clinical benefit to avoid steroid-dependence ~~when patients are unable to be weaned from steroids.~~

ICI_RENAL-1
- This page has been extensively revised.

IMMUNO-A 1 OF 3
- General Principles, new 4th bullet added: Combination therapies with non-ICI agents (eg. VEGF inhibitors) may complicate irAE workup due to overlapping toxicity. If low suspicion of irAE, consider holding non-ICI therapy and monitoring before use of immunosuppression.
- Principles of Steroid Use in the Management of irAEs
  - 5th bullet, 1st sub bullet modified: Longer steroid tapers (>4 weeks, sometimes 6–8 weeks or longer) may be required to prevent recurrent irAE events, particularly pneumonitis, hepatitis, *and neuromuscular toxicities.*
  - 6th bullet
    - 1st sub bullet
      - 1st sub sub bullet modified: ~~Prophylaxis against~~ Pneumocystis jirovecii pneumonia (PJP) prophylaxis *is recommended for patients expected to receive ≥20 mg daily prednisone equivalent for ≥4 weeks. Consider starting PJP prophylaxis if still steroid-dependent by the end of 2 weeks. Sulfamethoxazoletrimethoprim is preferred. For patients with a sulfa allergy, consider IV pentamidine. Avoid atovaquone due to risk of diarrhea particularly in patients with colitis, and avoid dapsone due to risk of hemolytic anemia*. ~~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.
      - 2nd sub sub bullet modified: *Other* fungal infections are rare, and the utility of ~~fungal~~ prophylaxis for these infections ~~during irAE management~~ is unclear. Patients receiving extended immunosuppression may be at higher risk of an invasive fungal infection.
    - 3rd sub bullet modified: Osteoporosis. If patients need to be on *steroids* long-term ~~steroids~~, they are at risk for developing osteoporosis.

IMMUNO-A 2 OF 3
- Sub heading removed: Principles of Anti-TNFα Agents and Other Immunosuppressants
- Bullet removed: Anti-TNFα agents (eg, infliximab or FDA-approved biosimilar) are particularly effective in management of immune-related colitis and inflammatory arthritis.
- Pathogen Reactivation
  - 1st bullet modified: There is a risk for hepatitis B virus (HBV) reactivation *with anti-TNFα agents,* ~~adalimumab, infliximab,~~ rituximab, or other immunosuppressive agents (eg, steroids).
- Indications for anti-TNFα Therapy section removed.

IMMUNO-A 3 OF 3
- Considerations for Organ Transplant Recipients, 1st bullet modified: 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. *The risks and benefits of ICI therapy in transplant patients are very complex. Please refer to transplant team prior to starting immunotherapy in such patients.*

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IMMUNO-C 1 OF 3

- This page has been extensively revised.

IMMUNO-C 2 OF 3

- Organ-Specific Considerations for Immunotherapy Rechallenge After a Hold
  - Liver
    - ◊ 1st bullet modified: Transaminitis without *synthetic liver dysfunction* ~~elevated bilirubin~~: Following a grade 2 irAE, *may* consider resumption of immunotherapy after ALT/AST return to baseline and steroids, if used, have been tapered to ≤10 mg prednisone equivalent daily.
    - ◊ Bullet removed: For grade 3 hepatitis, if on CTLA-4 combined with PD-1/PD-L1, restart with just PD-1/PD-L1 inhibitor.
    - ◊ 2nd bullet modified: *Permanently* discontinue immunotherapy in the setting of *G4* ~~severe or life-threatening (grade 4) hepatitis~~ *synthetic liver dysfunction and/or permanent biliary strictures requiring ERCP.*
  - Lung
    - ◊ 3rd bullet modified: Permanent discontinuation is warranted in the setting of severe (grade ~~3–~~4) pneumonitis.
  - Nervous System
    - ◊ 1st bullet modified: Myasthenia gravis: Permanently discontinue immunotherapy after grade ~~2~~ *3*–4 AE.
    - ◊ 2nd bullet modified: GBS: ~~permanently~~ Discontinue immunotherapy for ~~any~~ *severe (*grade *3-4)* GBS.
    - ◊ 5th bullet modified: Encephalitis: ~~Permanent~~ Discontinuation is warranted in the setting of ~~moderate to~~ severe encephalitis ~~(grade 2 –4)~~.
    - ◊ 6th bullet modified: Demyelinating disease: Discontinuation of immunotherapy following any-grade *AE* ~~transverse myelitis.~~

CART-1

- Post-CAR T-Cell Infusion, 6th bullet modified: Neurotoxicity assessment should be done at least twice daily *until hospital discharge, and urgently thereafter if there is a change in* ~~or when~~ the patient's status *or routinely* ~~changes~~ every 2–4 weeks, extending to 2 months. Consider a physical assessment and/or tests to check handwriting and general function/gait (eg, Timed Get Up and Go [TUG] test). If neurologic concern develops, more frequent assessments are recommended.

CART-2

- CRS
  - 4th bullet modified: Serious events may include hypotension, hypoxia, atrial fibrillation and ventricular tachycardia, cardiac arrest, cardiac failure, renal insufficiency, *and* capillary leak syndrome~~, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS).~~
- Neurologic Toxicity modified: Neurologic Toxicity*/Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)*
- Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome (HLH/MAS) changed to Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis- Like Syndrome (IECHS)
  - 1st bullet modified: Criteria for considering *IEC-HS* (previously called *Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome*
  - *[HLH/MAS])* ~~HLH/MAS~~:
    - ◊ 1st sub bullet modified: *Elevated ferritin (>2 x ULN or baseline (at time of infusion)) and/or rapidly rising (per clinical assessment)* ~~Rapidly rising and high ferritin (>5000 ng/mL) with cytopenias in the context of fever, especially if accompanied by any of the following: Grade ≥ 3 increase in serum bilirubin, AST, ALT, Grade ≥ 3 oliguria or increase in serum creatinine, Grade ≥ 3 pulmonary edema~~
    - ◊ 2nd sub bullet modified: ~~Presence of hemophagocytosis in bone marrow or organs based on histopathologic assessment of cell morphology and/or CD68 immunohistochemistry (IHC)~~ *For other criteria to identify IEC-HS, refer to: Hines et al. Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome. Transplantation and Cellular Therapy 2023;29438.e1-438.e16.*
- Footnote a modified: See Prescribing Information for each agent *and institutional protocols.*

CONTINUED
UPDATES

Terminologies in all NCCN Guidelines are being actively modified to advance the goals of equity, inclusion, and representation.

Updates in Version 1.2024 of the NCCN Guidelines for Management of Immunotherapy-Related Toxicities from Version 3.2023 include:

CART-3

• This page has been extensively revised.

CART-4

• New section added for Toxicities Specific To Anti-BCMA Car T-Cell Therapy.

CART-5A

• Footnote g modified: ~~For HLH/MAS, treat as per CRS with tocilizumab and steroids, although the suspicion of HLH/MAS should prompt consideration of higher doses of steroids at a given CRS grade. If no improvement is observed within 48 hours, consider addition of anakinra to steroids. Etoposide or intrathecal cytarabine can be considered as a last resort for HLH with CNS involvement.~~ *If IEC-HS is suspected, refer to treatment options in Hines, MR, Knight, TE, et al. Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome. Transplantation and Cellular Therapy* 2023;29(7)

• New footnote n added: An FDA-approved biosimilar is an appropriate substitute for tocilizumab. (Also for CART-7)

• Footnote p modified: Antifungal prophylaxis *and close monitoring for breakthrough infections per institutional guidelines* should be strongly considered in patients receiving steroids for the treatment of CRS and/or neurotoxicity. (Also for CART-7)

• Footnote u modified: *Anakinra may be considered as the first choice for severe CRS refractory to anti-IL6 therapy and high dose corticosteroids.* Other agents such as ~~anakinra,~~ siltuximab, ruxolitinib, cyclophosphamide, IVIG, ATG, intrathecal chemotherapy, or extracorporeal cytokine adsorption with continuous renal replacement therapy (CRRT) ~~might~~ *may also* be considered, *although*~~. Reported~~ experience with these agents is limited. Use of these therapies should be balanced against potential safety concerns, such as infection risk.

CART-7

• Assessment and Supportive Care Recommendations (all grades)

▸ Grade 4, 2nd bullet modified: High-dose steroids. *If unresponsive to steroids, consider adding anakinra 100 mg q 6 h.*

ENGAGE-1

• 2nd bullet modified: *CD3-based* lymphocyte engager therapies carry a universal risk of CRS. CRS risk requires frequent monitoring and early intervention to prevent progression to severe or refractory CRS.

PRINCIPLES OF ROUTINE MONITORING FOR IMMUNE-CHECKPOINT INHIBITORS

Pre-Therapy Assessment[a]	Monitoring Frequency[b]	Evaluation for Abnormal Findings/Symptoms
Clinical • Physical examination • Patient and relevant family history of any autoimmune/organ-specific disease, endocrinopathy, or infectious disease (ID). • Neurologic examination • Bowel habits (typical frequency/consistency) • Infectious disease screening (human immunodeficiency virus [HIV]; hepatitis A, B, C) as indicated	Clinical examination at each visit with adverse event (AE) symptom assessment	Follow-up testing based on findings, symptoms
Imaging • Cross-sectional imaging • Brain MRI if indicated	Periodic imaging as indicated	Follow-up testing as indicated based on imaging findings
General blood work • Complete blood count (CBC) (with differential if indicated) • Comprehensive metabolic panel (CMP)	Repeat prior to each treatment or every 4 weeks during immunotherapy, then in 6–12 weeks or as indicated	HbA1c for elevated glucose
Dermatologic (ICI_DERM-1) • Examination of skin and mucosa if history of immune-related skin disorder	Conduct/repeat as needed based on symptoms	Consider dermatology referral. Monitor affected skin and lesion type; photographic documentation. Skin biopsy if indicated.
Pancreatic (ICI_ENDO-1) • Baseline testing is not required	No routine monitoring needed if asymptomatic	Amylase, lipase, and consider abdominal CT with contrast or MRCP for suspected pancreatitis.
Thyroid (ICI_ENDO-2) • Thyroid-stimulating hormone (TSH), free thyroxine (T4)	Every 4–6 weeks during immunotherapy, then follow-up every 12 weeks as indicated	ICI_ENDO-2 and ICI_ENDO-3
Pituitary/Adrenal (ICI_ENDO-4) • Consider serum cortisol (morning preferred) and thyroid function as above	Consider repeating every 4–6 weeks during immunotherapy (immuno-oncology [IO] only regimens[c]), then follow-up every 12 weeks as indicated	Morning serum cortisol, adrenocorticotropic hormone (ACTH), TSH, T4, luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, estradiol (premenopausal individuals), and cosyntropin stimulation test only as indicated.

[a] Prior to initiating treatment, counsel patients and caregivers on the warning signs and symptoms of immune-related adverse events (irAEs). Principles of Immunotherapy Patient Education (IMMUNO-B). For guidance on general recommendations for vaccination in patients with cancer, see NCCN Guidelines for the Prevention and Treatment of Cancer-Related Infections.

[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] For regimens that require steroid premedication, routine surveillance is not recommended.

Continued

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PRINCIPLES OF ROUTINE MONITORING FOR IMMUNE-CHECKPOINT INHIBITORS

Pre-Therapy Assessment[a]	Monitoring Frequency[b]	Evaluation for Abnormal Findings/Symptoms
Pulmonary (ICI_PULM-1) • Oxygen saturation (resting and with ambulation) • Consider pulmonary function tests (PFTs) with diffusion capacity for patients who are high risk (eg, interstitial lung disease on imaging, chronic obstructive pulmonary disease (COPD), previous suspected treatment-related lung toxicity) • In the absence of prior imaging, consider a chest x-ray	Repeat oxygen saturation tests based on symptoms	Chest CT with contrast to evaluate for pneumonitis, biopsy, or bronchoscopy with bronchoalveolar lavage (BAL) if needed to exclude other causes.
Cardiovascular (ICI_CARDIO-1) • Consider baseline electrocardiogram (ECG) • Individualized assessment in consultation with cardiology as indicated	Consider periodic testing for those with abnormal baseline or symptoms	Individualized follow-up in consultation with cardiology as indicated
Musculoskeletal (ICI_MS-1) • Joint examination/functional assessment as needed for patients with pre-existing disease	No routine monitoring needed if asymptomatic	Consider rheumatology referral. Depending on clinical situation, consider C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), or creatine kinase (CK)

[a] Prior to initiating treatment, counsel patients and caregivers on the warning signs and symptoms of immune-related adverse events (irAEs). Principles of Immunotherapy Patient Education (IMMUNO-B). For guidance on general recommendations for vaccination in patients with cancer, see NCCN Guidelines for the Prevention and Treatment of Cancer-Related Infections.

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

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CONDITIONS	SIGNS AND SYMPTOMS (MAY INCLUDE ONE OR MORE)
CARDIO: Myocarditis	Chest pain, shortness of breath, fatigue, palpitations (arrhythmia: heart block or ventricular ectopic beats), syncope, generalized weakness. This adverse event may occur in conjunction with myositis and/or myasthenia gravis; these entities must be ruled out.
DERM: Bullous dermatitis	Inflammation of the skin and the presence of bullae, which are filled with fluid. The most common immune-related bullous dermatitis is bullous pemphigoid. May be intense or widespread; intermittent; skin changes from scratching (eg, edema, excoriations, lichenification, oozing/crusts); limiting instrumental activities of daily living (iADLs).
DERM: Maculopapular rash (morbilliform rash)	Macules (flat) and papules (elevated)
DERM: Pruritus	Itching sensation, with or without rash
DERM: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)	SJS, overlapping SJS/TEN, and TEN are characterized by separation of the dermis involving <10%, 10%–30%, and >30% body surface area (BSA), respectively
DERM: Lichen planus	Violaceous (dark red/purple) papules and plaques without scale over the trunk and extremities, significant pruritus. Erosions and striae (white lines intersecting) in the oral and vulvar mucosa.
DERM: Psoriasis and psoriasiform disease	Thick red scaly plaques, accentuated on extensor surfaces, scalp, umbilicus, postauricular surfaces
DERM: Oral mucosa inflammation	Irritated gums and/or oropharynx, red/white lesions and/or ulcers, lichen planus, mucositis
DERM: Dry mouth (Sicca syndrome)	Dry mouth, oral sensitivity, dysarthria, dysphagia, dysgeusia, dental caries/erosion with prolonged salivary hypofunction, dry eye, lack of lubrication
DERM: Oral dysesthesia	Pain most often described as "burning" in the absence of, or disproportionate to, skin changes, oral sensitivity, dysgeusia, phantogeusia, or other altered sensation with normal clinical findings
ENDO: Hyperglycemia-related diabetic ketoacidosis (DKA)	Excessive thirst, frequent urination, general weakness, vomiting, confusion, abdominal pain, dry skin, dry mouth, increased heart rate, and fruity odor on the breath
ENDO: Overt hypothyroidism	Fatigue, lethargy, sensation of being cold, possible constipation
ENDO: Thyrotoxicosis due to thyroiditis	Most patients with thyrotoxicosis due to thyroiditis have minimal, if any symptoms. If symptoms do arise, may include uncommonly, tachycardia, tremor, anxiety, enlarged and tender thyroid gland (rarely).
ENDO: Hypophysitis	Acute onset headache, photophobia, nausea/emesis, fatigue, muscle weakness, may have low blood pressure
ENDO: Primary adrenal insufficiency	High ACTH with low morning cortisol, abnormal cosyntropin stimulation test. This is a rare diagnosis not usually associated with checkpoint immunotherapy.

Continued

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CONDITIONS	SIGNS AND SYMPTOMS (MAY INCLUDE ONE OR MORE)
ENDO: Central hypothyroidism	Symptoms of overt hypothyroidism (fatigue, lethargy, sensation of being cold, possible constipation) plus symptoms of central adrenal insufficiency (nausea/emesis, not feeling well, generalized malaise).
GI: Colitis	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 gastrointestinal (GI) bleeding, including peptic ulcer disease (PUD) and malignant bleeding.
GI: Transaminitis	Elevated alanine transaminase (ALT) and aspartate transaminase (AST)
GI: Cholestasis	Elevated alkaline phosphatase (predominant) with or without bilirubin/AST/ALT elevation.
GI: Pancreatitis	Acute pancreatitis: epigastric pain, nausea, possible vomiting Chronic pancreatitis: chronic abdominal pain, deficiency in pancreatic enzyme production with possible malabsorption
MUSCULO: Inflammatory arthritis	Joint pain, joint swelling; inflammatory symptoms: stiffness after inactivity, improvement with activity
MUSCULO: Myositis	Myositis is characterized by inflammation and/or weakness involving the skeletal muscles. This adverse event may occur in conjunction with myocarditis and/or myasthenia gravis; these entities must be ruled out. Common presenting symptoms may include muscle weakness, elevated creatinine kinase (CK), elevated transaminases, and myalgias.
MUSCULO: Polymyalgia rheumatica (PMR)	PMR symptoms: fatigue and/or muscle and joint pain typically in shoulders and hips
MUSCULO: Giant cell arteritis (GCA)	Visual symptoms, headache, scalp tenderness, jaw claudication
NEURO: Aseptic meningitis	Headache, photophobia, and neck stiffness, often afebrile but may be febrile. There may be nausea/vomiting. Mental status should be normal (distinguishes from encephalitis).
NEURO: Encephalitis	Confusion, altered behavior, headaches, seizures, short-term memory loss, depressed level of consciousness, focal weakness, and speech abnormality
NEURO: Guillain-Barré syndrome (GBS)	Progressive, most often symmetrical, ascending 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.
NEURO: Myasthenia gravis	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, which must be ruled out. Respiratory symptoms may require evaluation to rule out pneumonitis. Miller Fisher variant of GBS has overlapping symptoms (ophthalmoplegia and ascending weakness).

Continued

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CONDITIONS	SIGNS AND SYMPTOMS (MAY INCLUDE ONE OR MORE)
NEURO: Peripheral neuropathy	Asymmetric or symmetric sensory-motor deficit. Sensory deficit may be painful or painless paresthesias or potentially life-threatening autonomic (eg, myenteric plexus) dysfunction. Hypo- or areflexia. Isolated sensory deficit or sensory plus lower motor neuron deficit. GI tract paresis due to myenteric neuritis is a rare toxicity associated with immune checkpoint inhibitor (ICI) therapy. The presentation may be fulminant with profound ileus.
NEURO: ADEM (acute demyelinating encephalomyelitis)	Headache, confusion, seizures, depressed level of consciousness, speech abnormality, focal weakness, sensory change (numbness or tingling), ataxia/loss of balance, or vision loss.
NEURO: Optic neuritis	Vision loss, eye pain, decreased visual acuity, visual field loss, dyschromatopsia, relative afferent pupillary defect, optic disc edema
NEURO: Transverse myelitis	Acute or subacute weakness or sensory changes bilaterally, often with bowel/bladder changes and spinal level to pinprick, hyperreflexia, positive Babinski.
OCULAR: Vision changes	Blurred/distorted vision, new floaters, itchy eyes, blind spots, change in color vision, photophobia, tenderness/pain, eyelid swelling, and proptosis. Episcleritis can be associated with red discoloration of the eye. Uveitis can be associated with eye redness.
PULM: Pneumonitis	Dry cough, shortness of breath, fever, chest pain
RENAL: Acute kidney injury (AKI)	Elevation of creatinine/blood urea nitrogen (BUN), inability to maintain acid/base or electrolyte balance, and urine output change (usually decreased)

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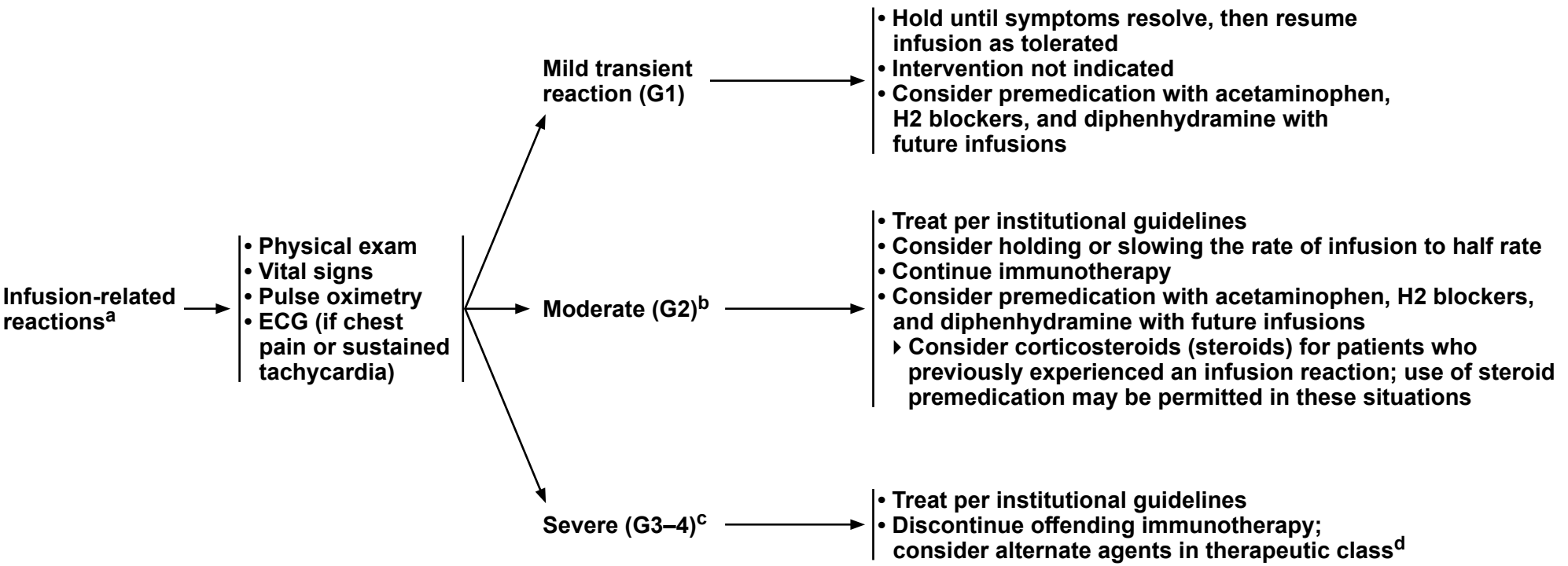

[a] Symptoms include: Fever/chills/rigors, back pain, urticaria/pruritus, angioedema, flushing/headache, hypertension, hypotension, shortness of breath, cough/wheezing, hypoxemia, dizziness/syncope, sweating, and arthralgia/myalgia. Refer to prescribing information for each individual immunotherapy agent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

[b] Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs], narcotics, intravenous [IV] fluids); prophylactic medications indicated for ≤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.

[d] If infusion reactions that are resistant to standard therapy occur in patients receiving programmed death ligand 1 (PD-L1) inhibitors, consider switching to a programmed cell death protein 1 (PD-1) inhibitor for subsequent treatments. There are no data to guide the use of alternate ICIs.

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CARDIOVASCULAR ADVERSE EVENT(S)

SYMPTOMS/SIGNS

- Ventricular arrhythmias/ tachycardia
- Conduction abnormalities/heart block
- Heart failure
- Cardiogenic shock
- Pericardial effusion

Suspected myocarditis/ Pericarditis/ Large vessel vasculitis[a] →

- Differential
  - Myocardial infarction/ acute coronary syndrome
  - Myositis/myasthenia gravis[b]
  - Pulmonary embolism (PE); malignant involvement
  - Other infectious etiologies, COVID-19, post- vaccinations AEs

ASSESSMENT/GRADING

- Immediate cardiology consultation (preferably cardio-oncology)
- ECG (compare to baseline for any suspected cardiovascular AE)
- Telemetry monitoring (inpatient)/topical patch monitor (outpatient)
- Echocardiogram (if possible with left ventricular (LV) strain measurement)
- Cardiac biomarkers (troponin I or T, CK,[c] BNP, or NTproBNP; lipid panel[d])
- Inflammatory biomarkers[e]
- Cardiac MRI with and without contrast (if possible)[f]
- Consider cardiac catheterization and/or myocardial biopsy as clinically indicated
- Consider viral titers

MANAGEMENT[g]

Myocarditis →

- Discontinue immunotherapy[h]
- Management is tailored to response and acuity of presentation
- High-dose steroids such as IV methylprednisolone 1 g/day for 3–5 days
  - If responding and stable, switch to oral prednisone (1 mg/kg/day), then taper slowly over 6–12 weeks based on clinical response and improvement of biomarkers
- If no improvement within 24–48 hours on steroids, initiate additional immunosuppression (listed in alphabetical order):
  - Abatacept
  - Alemtuzumab[i]
  - Antithymocyte globulin (ATG)
  - Infliximab[i,j] (use with extreme caution in patients with reduced left ventricular ejection fraction [LVEF])
  - Intravenous immunoglobulin (IVIG)[k]
  - Methotrexate
  - Mycophenolate[l]
  - Plasmapheresis
- Abatacept with ruxolitinib has been used in concomitant myositis and myocarditis[m]
- ICU-level monitoring
- Temporary or permanent pacing as required

Pericarditis/ Pericardial effusion →

- Consider myocarditis as a contributor
- If myocarditis not present, manage as per usual recommendations[n]

Footnotes on ICI_CARDIO-1A

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FOOTNOTES

[a] Myocarditis symptoms are nonspecific and may occur as early as days to weeks after 1–2 doses of ICI. Although rare, myocarditis is often severe and associated with myositis/myasthenia gravis (3 M's), and more common with combination therapy. In most fatal cases, conduction abnormalities were the cause of death, and ejection fraction was preserved.
[b] This can also be associated with thymoma.
[c] To assess for associated myositis.
[d] Lipid panel would be recommended at baseline to assess cardiovascular risk. Also consider troponin and NTproBNP at baseline for identifying those at increased risk. Also, consider high-sensitivity troponin and NTproBNP at baseline and serially during treatment to detect abnormal blood biomarkers that may precede symptomatic myocarditis induced by ICI.
[e] Consider ESR, CRP, or other inflammatory markers.
[f] Use of multiparameter tissue characterization by MRI, including T1 and T2 mapping and application of modified Lake Louise Criteria provides important diagnostic value for myocarditis. If cardiac MRI is negative or myocarditis is highly suspected, consider endomyocardial biopsy.
[g] Principles of Immunosuppression (IMMUNO-A).
[h] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[i] Perform a TB blood test (eg, T-Spot/QuantiFERON tuberculosis [TB] gold) (depending on facility) and hepatitis testing at time of suspected toxicity to facilitate administration.
[j] An FDA-approved biosimilar is an appropriate substitute for infliximab.
[k] Total dosing should be 2 g/kg, administered in divided doses per package insert.
[l] Mycophenolate mofetil treatment (0.5–1 g every 12 h).
[m] Salem JE, et al. Cancer Discov 2023;13:1100-1115.
[n] Adler Y, et al. Eur Heart J 2015;36:2921-2964.

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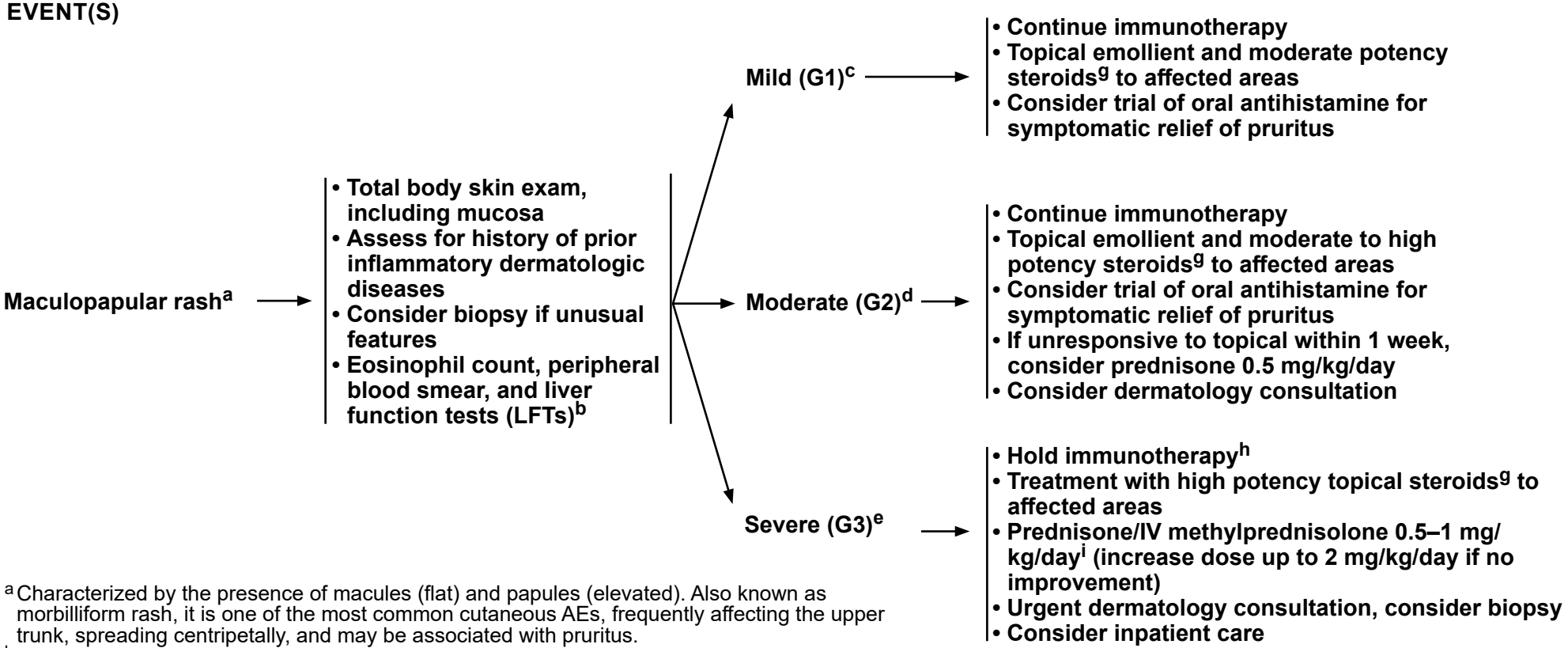

[a] Characterized by the presence of macules (flat) and papules (elevated). Also known as morbilliform rash, it is one of the most common cutaneous AEs, frequently affecting the upper trunk, spreading centripetally, and may be associated with pruritus.

[b] These features can be used to assist with the diagnosis of DRESS (drug rash with eosinophilia and systemic symptoms) syndrome. This syndrome is typically characterized by a maculopapular rash that involves the face and ears and typically presents with swelling of the face and hands within 2–8 weeks after drug exposure. Note that certain classes of high-risk medications initiated in the prior few weeks may also cause maculopapular rash, including antiepileptic drugs: carbamazepine, phenytoin, lamotrigine, phenobarbital; antihyperuricemics: allopurinol, febuxostat; sulfonamides and sulphones: trimethoprim sulfamethoxazole, sulfasalazine, dapsone; and other antibiotics: vancomycin, minocycline, other beta-lactams. Kardaun SH, et al. Br J Dermatol 2013;169:1071-1080.

[c] Macules/papules covering <10% BSA with or without symptoms (eg, pruritus, burning, tightness).

[d] Macules/papules covering 10%–30% BSA with or without symptoms (eg, pruritus, burning, tightness); limiting iADLs.

[e] Macules/papules covering >30% BSA with or without associated symptoms; limiting self-care activities of daily living (ADLs).

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

[g] Topical steroids by potency: High (eg, clobetasol 0.05% or fluocinonide 0.05% [cream or ointment]); Moderate (eg, triamcinolone 0.1% [cream, ointment, lotion] or betamethasone valerate [lotion]).

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

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

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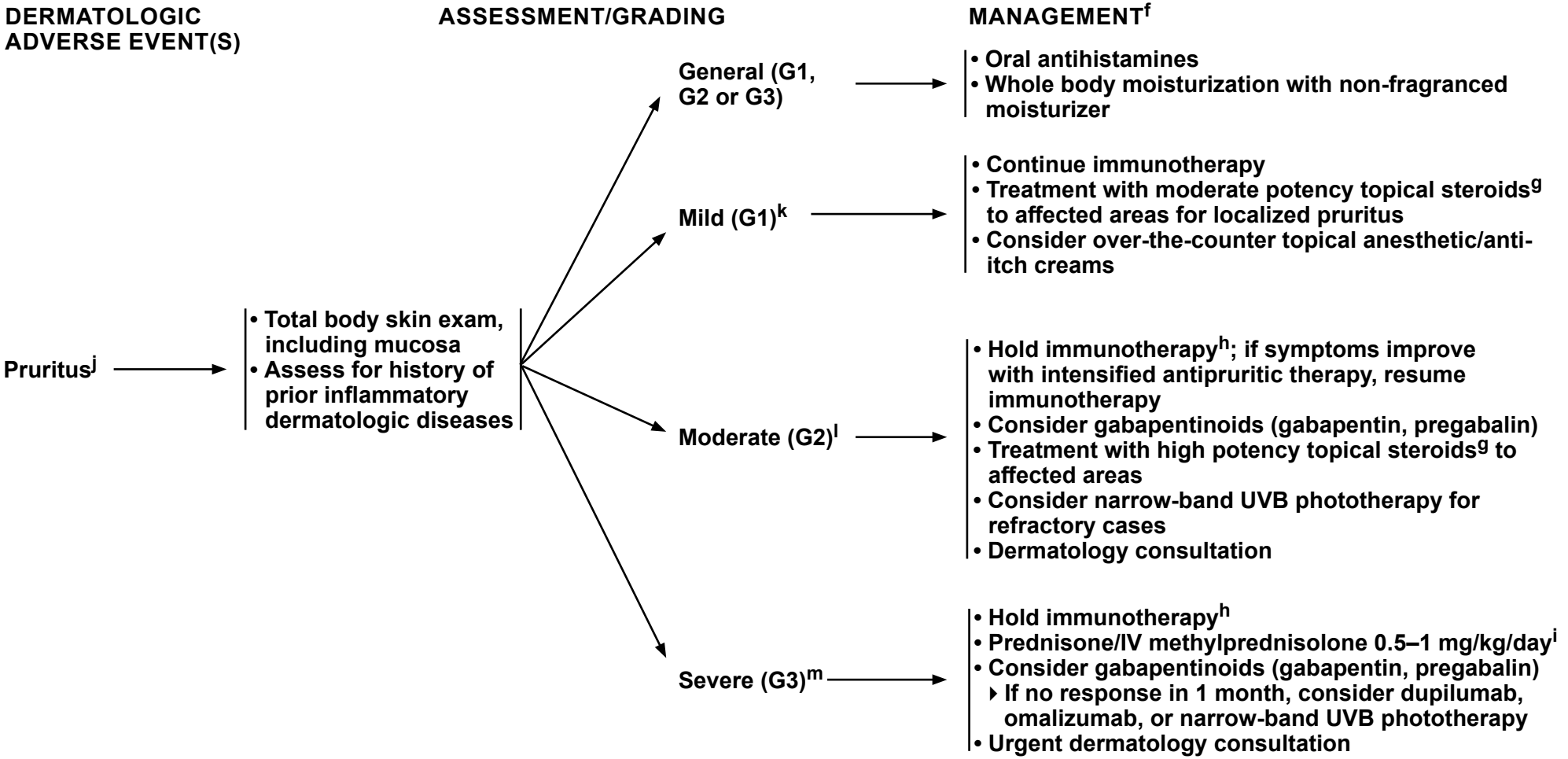

[f] Principles of Immunosuppression (IMMUNO-A).
[g] Topical steroids by potency: High (eg, clobetasol 0.05% or fluocinonide 0.05% [cream or ointment]); Moderate (eg, triamcinolone 0.1% [cream, ointment, lotion] or betamethasone valerate [lotion]).
[h] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[i] Treat until symptoms improve to Grade ≤1, then taper over 4–6 weeks.
[j] Characterized by an intense itching sensation with or without rash.
[k] Mild or localized.
[l] Intense or widespread; intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); limiting iADLs.
[m] 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.

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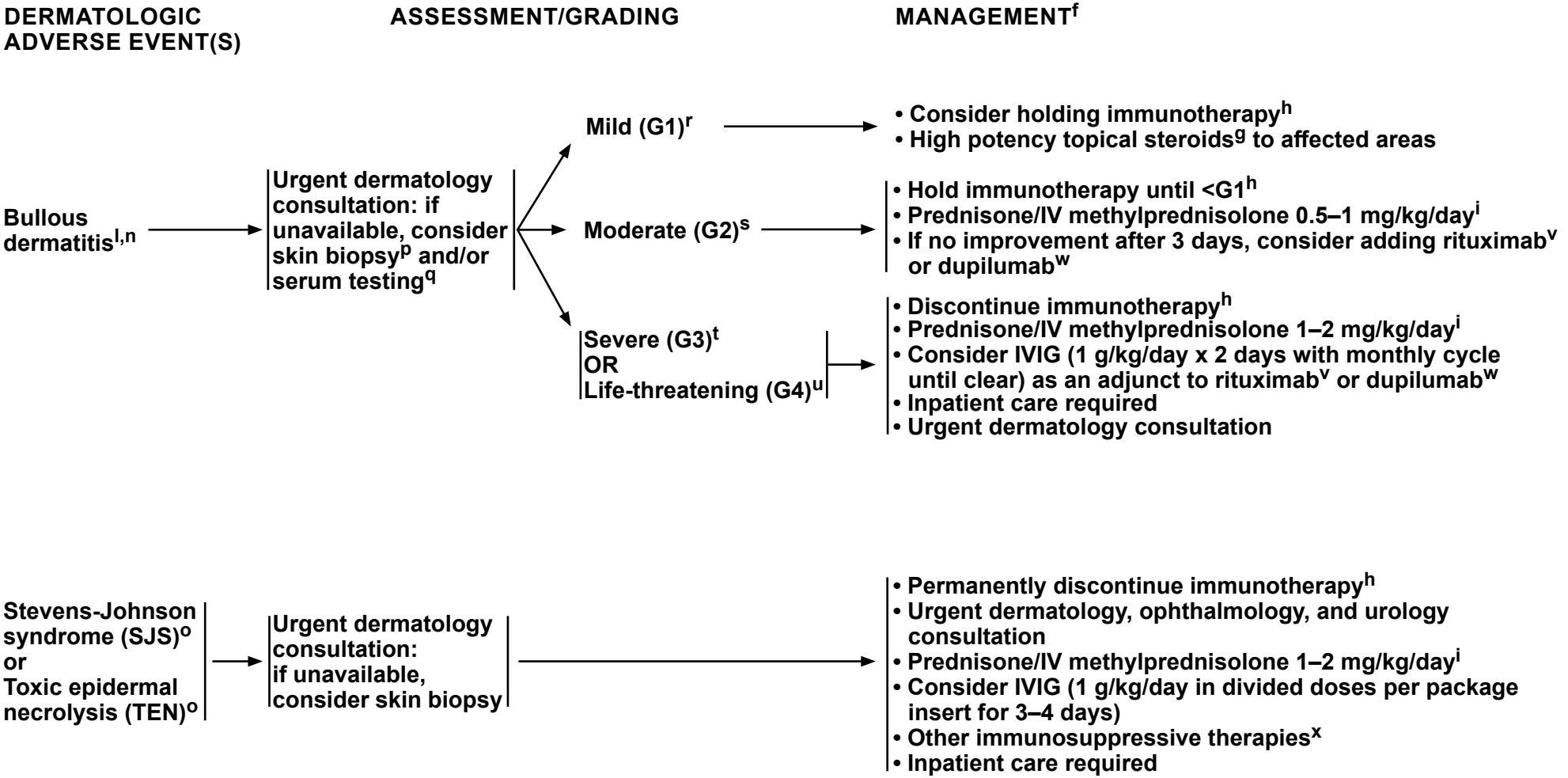

Footnotes on ICI_DERM-3A

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FOOTNOTES

[f] Principles of Immunosuppression (IMMUNO-A).
[g] Topical steroids by potency: High (eg, clobetasol 0.05% or fluocinonide 0.05% [cream or ointment]); Moderate (eg, triamcinolone 0.1% [cream, ointment, lotion] or betamethasone valerate [lotion]).
[h] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[i] Treat until symptoms improve to Grade ≤1, then taper over 4–6 weeks.
[l] 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 should be performed on perilesional intact skin. Two biopsies should be performed with one being sent for direct immunofluorescence testing in Michel's media, if available, or in normal saline (if Michel's media not available).
[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] 1000 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, et al. Lancet 2017;389:2031-2040. An FDA-approved biosimilar is an appropriate substitute for rituximab.
[w] Shipman WD, et al. Br J Dermatol. 2023;189:339-341.
[x] Immunosuppressive therapies (ie, IVIG, etanercept or biosimilar, cyclosporine) can be considered. After a patient has widespread skin separation (blisters or erosions), the risk of infection should be weighed against the potential benefits of immunosuppression.

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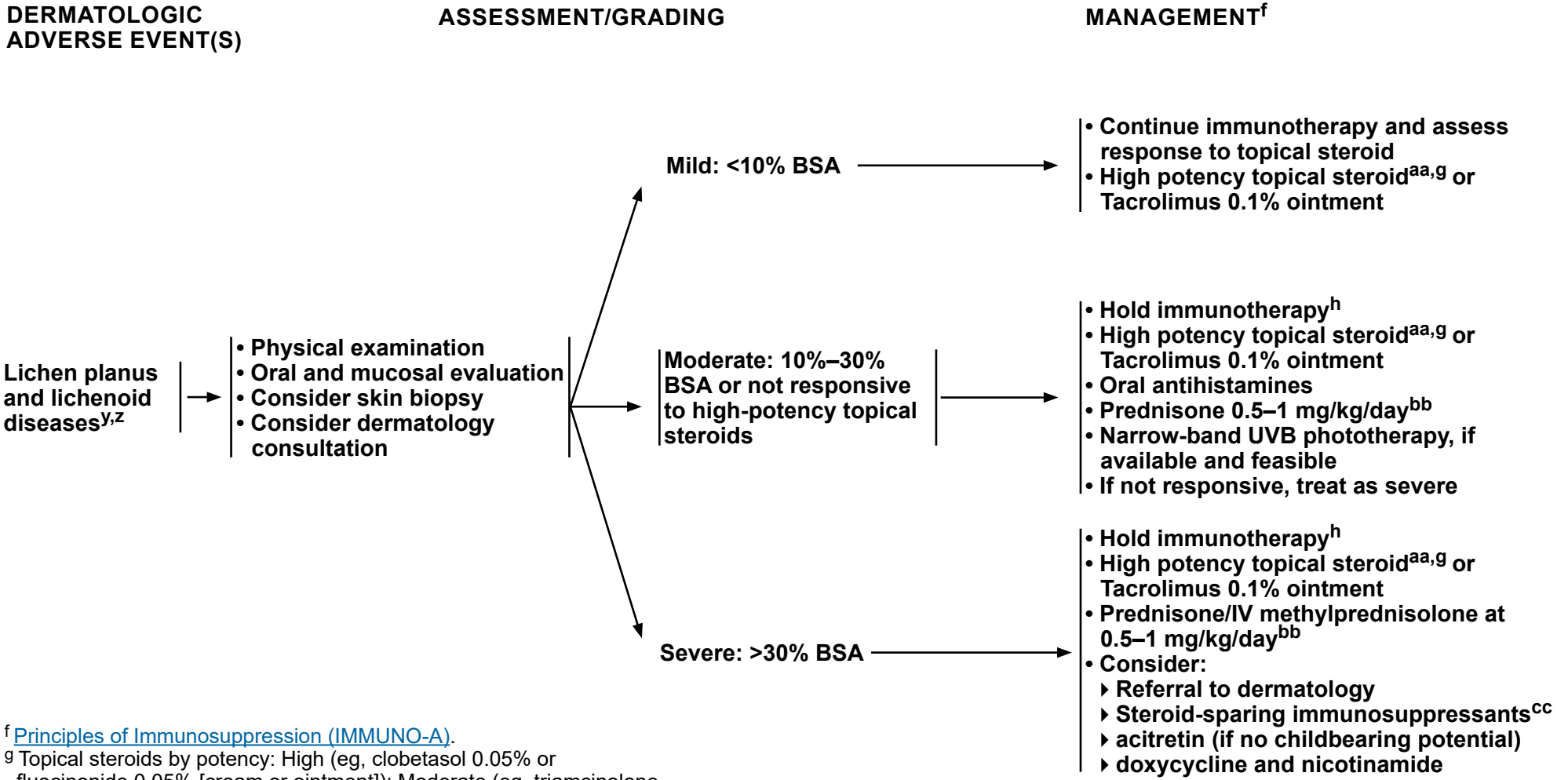
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[f] Principles of Immunosuppression (IMMUNO-A).
[g] Topical steroids by potency: High (eg, clobetasol 0.05% or fluocinonide 0.05% [cream or ointment]); Moderate (eg, triamcinolone 0.1% [cream, ointment, lotion] or betamethasone valerate [lotion]).
[h] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[y] Shi VJ, et al. JAMA Dermatol 2016;152:1128-1136; Masterson WM, et al. Cancer Treat Res Commun 2022;30:100506.
[z] Violaceous (dark red/purple) papules and plaques without scale over the trunk and extremities, significant pruritus. Erosions and striae (white lines intersecting) in the oral and vulvar mucosa.
[aa] Consider gel for mucosal disease, solution for scalp disease, and cream/lotion/ointment for other affected areas.
[bb] Treat until symptoms improve to Grade 1 then taper over 3 weeks.
[cc] Azathioprine, cyclosporine, hydroxychloroquine, methotrexate, and mycophenolate mofetil.

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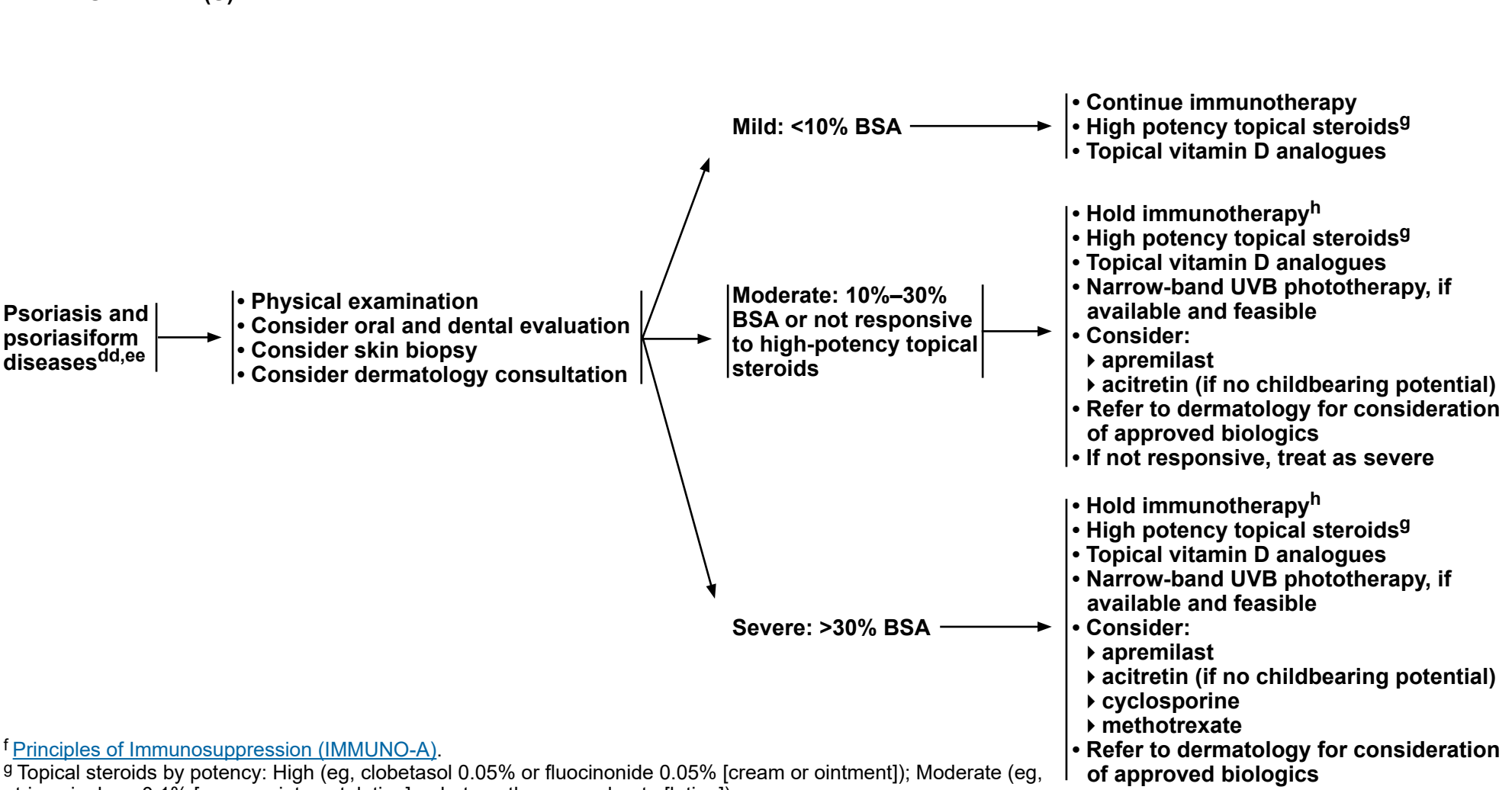

[f] Principles of Immunosuppression (IMMUNO-A).
[g] Topical steroids by potency: High (eg, clobetasol 0.05% or fluocinonide 0.05% [cream or ointment]); Moderate (eg, triamcinolone 0.1% [cream, ointment, lotion] or betamethasone valerate [lotion]).
[h] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[dd] Nikolaou V, et al. J Am Acad Dermatol 2021;84:1310-1320; Said JT, et al. J Am Acad Dermatol 2022;87:399-400.
[ee] Thick, red scaly plaques, accentuated on extensor surfaces, scalp, umbilicus, and postauricular surfaces.

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ORAL MUCOSA ADVERSE EVENT(S)

ASSESSMENT/GRADING

MANAGEMENT[f]

Oral mucosa inflammation[ff]

- Comprehensive mucosal exam
- Assess for primary oral inflammation disease
- Pain score/alimentation limitations
- Consider mucosal biopsy for histopathology and direct immunofluorescence
- Evaluate for skin blistering[gg]
- Fungal and viral swab of oral erosion for HSV PCR and Candida culture
- Assess contribution of cytotoxic agents in combination regimens

General

- Dietary modifications[hh]
- Good oral hygiene (eg, chlorhexidine oral rinse)
- If available, referral to:
  - Dermatology/Oral Medicine
  - Dental[ii]
  - ENT[jj]

Mild (G1): some food restrictions

- Continue immunotherapy
- Acid suppression[kk]
- High potency topical steroids (oral liquid or gel formulation)[ll]
- Topical anesthetics[mm]

Moderate (G2): soft/pureed foods only

- Hold immunotherapy[h]
- High[ll] to very-high[nn] potency topical steroids (oral liquid or gel formulation)
- Tacrolimus 0.1% ointment (or compounded solution) for lips; may combine with topical steroids intraorally
- Prednisone or IV methylprednisolone 0.5–1 mg/kg/day[bb]
- Lip/oral biopsy, if clinically indicated and not previously done

Severe (G3–4): unable to eat

- Hold immunotherapy[h]
- Inpatient care
- Very-high[nn] potency topical steroids (oral liquid or gel formulation)
- Prednisone or IV methylprednisolone 1–2 mg/kg/day[bb]
- Lip/oral biopsy, if clinically indicated and not previously done

Footnotes on ICI_DERM-6A

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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.

FOOTNOTES

[f] Principles of Immunosuppression (IMMUNO-A).
[h] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[bb] Treat until symptoms improve to Grade 1 then taper over 3 weeks.
[ff] Irritated gums and/or oropharynx, red/white lesions and/or ulcers, lichen planus, or mucositis; for management of lichen planus, see ICI_DERM-4.
[gg] Consider testing for autoimmune blistering disease pemphigus (Anti-Desmoglein 1 and 3) and bullous pemphigoid (Anti-Bullous Pemphigoid Antigen 1 and 2). If immunologic tests confirm autoimmune disease, see blistering disorders on ICI_DERM-3.
[hh] Avoid crunchy, spicy, acidic, or hot food/drink as appropriate for comfort.
[ii] To ensure adequate hygiene and protect against the risk of dental caries; consider if mild and strongly consider if moderate or severe inflammation.
[jj] Assist in the management of persistent mucositis or if oropharynx/larynx involved; consider if mild or strongly consider if moderate or severe (especially if airway involved).
[kk] Proton pump inhibitor (PPI) or H2 blockade.
[ll] Eg, Liquid dexamethasone 0.5 mg/5 mL elixir or fluocinonide 0.05% gel.
[mm] Magic mouthwash (equal parts diphenhydramine, antacid, and viscous lidocaine).
[nn] Eg, Clobetasol 0.05% gel, compounded budesonide 3 mg/10 mL solution.

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ORAL MUCOSA ADVERSE EVENT(S)	ASSESSMENT/GRADING		MANAGEMENT[f]
Dry mouth (Sicca syndrome[oo])	• Review medication profile and avoid medications that contribute to dry mouth • Assess hydration status • Check salivary pooling in floor of mouth • Assess thickness of saliva • Evaluate dentition and gum recession • Anti-SS-A and anti-SS-B • Antinuclear antibody (ANA)	Mild (G1)[qq]	• Continue immunotherapy • Dietary modifications[hh] • Improve hydration and limit caffeine intake • Topical measures (water sips, saliva substitutes, and moisture-preserving mouth rinses, toothpaste, or spray) • Salivary stimulants (sugarless chewing gum, lozenges, or candy)
		Moderate (G2)/ severe (G3)[rr]	• Hold immunotherapy[h] • Dietary modifications[hh] • Additional topical measures (saliva substitutes, mouth rinses or sprays) • Prednisone at 20–40 mg daily for 2–4 weeks, then taper[uu] • Systemic sialagogues (cevimeline or pilocarpine) • Rheumatology referral • Dental referral[vv] • Consider inpatient care for severe cases
Oral dysesthesia[pp]	• Assess location and character of pain • Rule out odontogenic or mucosal source • Assess severity of pain and impact on function	Mild (G1)[ss]	• Continue immunotherapy • Dietary modifications[hh] • Topical steroids (gel or dental paste preferred) or viscous lidocaine
		Moderate (G2)/ severe (G3)[tt]	• Hold immunotherapy[h] • Dietary modifications[hh] • Gabapentin, high potency topical steroids (gel or dental paste preferred), or viscous lidocaine

Footnotes on ICI_DERM-7A

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FOOTNOTES

[f] Principles of Immunosuppression (IMMUNO-A).
[h] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[hh] Avoid crunchy, spicy, acidic, or hot food/drink as appropriate for comfort.
[oo] Sicca syndrome is distinct from Sjogren's syndrome, with an abrupt onset of dry mouth, usually without dry eyes. Dry mouth from sicca syndrome may be partially improved with steroids but usually will require chronic care for salivary dysfunction. Warner BM, et al. Oncologist 2019;24:1259-1269.
[pp] Pain most often described as "burning" in the absence of, or disproportionate to, skin changes, oral sensitivity, dysgeusia, phantogeusia, or other altered sensation with normal clinical findings.
[qq] Dry or thick saliva only; minimal food restrictions.
[rr] Need for copious fluids to clear mouth of dry food; diet limited to soft, moist or pureed foods; or unable to eat; need for oral lubricants.
[ss] Mild discomfort; not interfering with oral intake.
[tt] Moderate (G2): interfering with oral intake; Severe (G3): disabling pain; tube feeding or total parenteral nutrition [TPN] indicated.
[uu] If prednisone results in initial improvement, consider dose escalation before tapering. If symptoms worsen, escalate to 0.5–1 mg/kg daily; if no improvement after 14 days at higher dose, reversal unlikely.
[vv] To ensure adequate hygiene and protect against the risk of dental caries. Patients with severe sicca syndrome can lose their teeth due to the severity of dry mouth and loss of salivary protection.

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ENDOCRINE ADVERSE EVENT(S)

Hyperglycemia[a,b]
- **New-onset fasting glucose >200 mg/dL[e] OR**
- **Random blood glucose >250 mg/dL OR**
- **History of type 2 diabetes mellitus (DM) with fasting/ random glucose >250 mg/dL**

DIAGNOSIS/WORKUP[c]
- **Consider new-onset ICI-associated type 1 DM (ICI-T1DM)[f]**
- **C-peptide with repeat serum glucose**
- **Evaluate for DKA[d] per institutional guidelines**
  - **Blood pH, basic metabolic panel, urine or serum ketones (eg, beta hydroxybutyrate)**
- **Consider measurement of autoantibodies (eg, anti-GAD, anti-islet cell, IA-2, anti-insulin, ZnT8)[f]**

C-peptide low (consistent with ICI-T1DM)[f,g,h]

DKA present →
- **Urgent endocrine consultation**
- **Inpatient care**
- **Hold immunotherapy until DKA resolves[i]**
- **Manage DKA as per institutional guidelines[j]**
- **Initiate insulin, as directed by inpatient team or endocrinologist, and close glucose monitoring (consider early use of continuous glucose monitoring [CGM])**

DKA not present →
- **Urgent endocrine consultation, consider inpatient care**
- **Initiate insulin and close glucose monitoring consistent with T1DM, as directed by endocrinologist**
- **Continue immunotherapy**

C-peptide appropriate for serum glucose →
- **Continue monitoring of serum glucose and consider HgbA1c**
- **Continue immunotherapy**
- **Consider insulin resistance (T2DM) or steroid-related[c] hyperglycemia**
- **Medical therapy, diet, and lifestyle interventions as per institutional guidelines**

[a] Elevated fasting glucose <200 mg/dL should be managed per national/ institutional guidelines and/or by a patient's primary care physician (PCP) or endocrinologist.
[b] Fasting glucose is preferred.
[c] High-dose steroids may induce or exacerbate hyperglycemia. Consider endocrinology referral and appropriate management if symptomatic and/or persistently uncontrolled.
[d] 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.
[e] In patients who are critically ill/ill-appearing with glucose >200 mg/dL (typically 300–500 mg/dL), urgent/emergent evaluation for DKA is indicated.
[f] The development of ICI-T1DM can be life-threatening if insulin therapy is not provided. Once new type 1 DM is diagnosed, management and monitoring should be directed by endocrinology team. ICI-T1DM may be permanent. Autoantibodies are not required for diagnosis. Empiric treatment as T1DM recommended if c-peptide unknown.
[g] Evaluate for signs/symptoms of pancreatic exocrine insufficiency, and supplement if needed.
[h] Insufficient evidence to suggest steroids may reverse ICI-T1DM, and may complicate glycemic control.
[i] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[j] 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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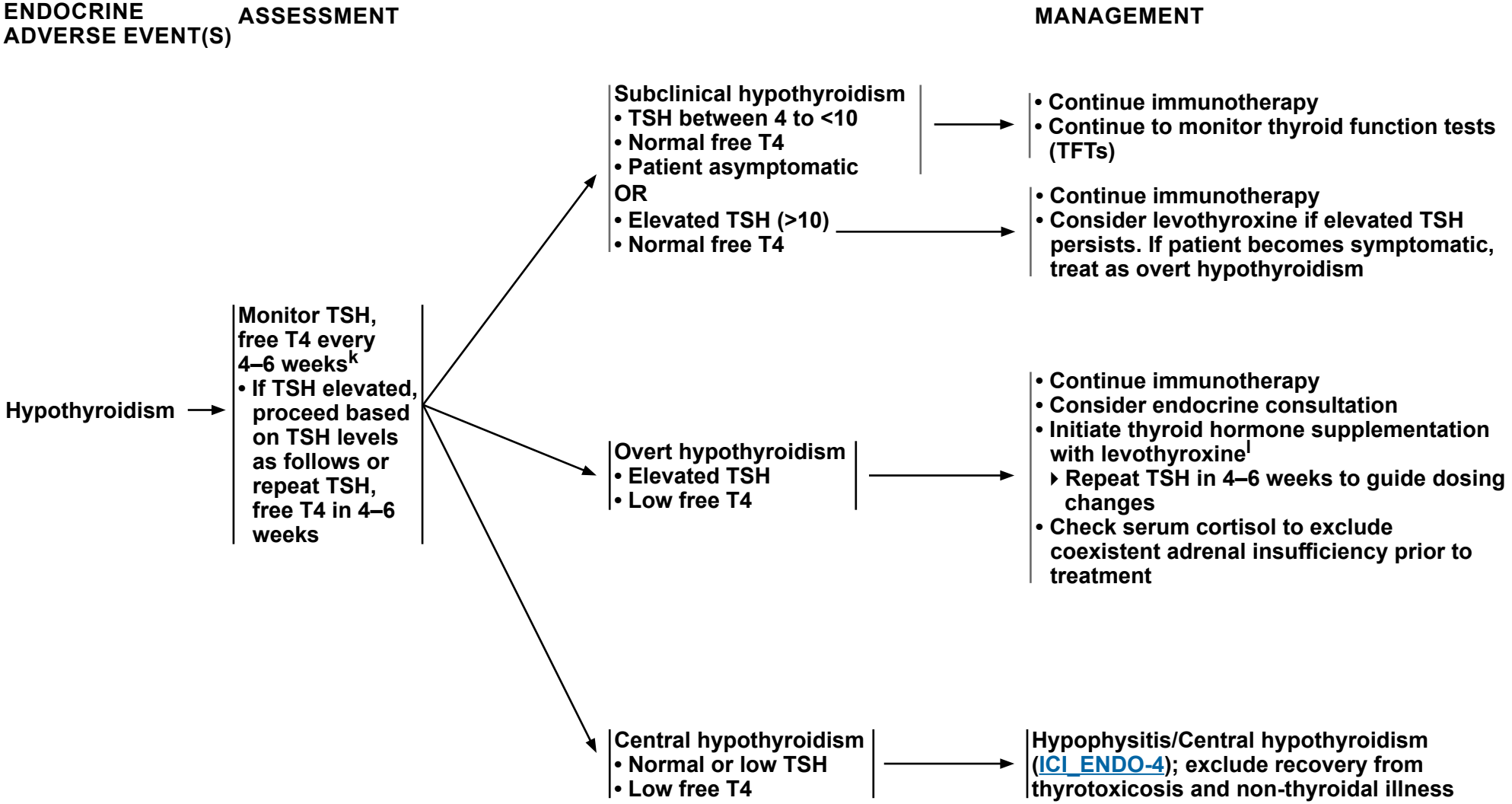

[k] For patients without baseline thyroid function abnormalities or who are asymptomatic, can increase TFT interval to every 12–18 weeks as indicated.
[l] Levothyroxine oral 1.2–1.4 mcg/kg/day. For patients with advanced age, cardiac risk, or prolonged hypothyroidism, initiate at 0.8–1.0 mcg/kg/day.

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ENDOCRINE ADVERSE EVENT(S)	ASSESSMENT	MANAGEMENT[n]
Thyrotoxicosis[m]	• Low or suppressed TSH with high free T4/total T3 • Consider endocrine consultation if symptomatic	• Continue immunotherapy if asymptomatic • Consider propranolol (10–20 mg every 4–6 hours for symptoms as needed) or atenolol or metoprolol as needed for symptoms until thyrotoxicosis resolves • Repeat TFTs in 4–6 weeks ▸ If resolved, no further therapy for thyrotoxicosis. Thyrotoxicosis often evolves to hypothyroidism (50%–90%) requiring treatment with thyroid hormone replacement (see Overt hypothyroidism on ICI_ENDO-2 for levothyroxine dosing) ▸ If persistent thyrotoxicosis, consider evaluation for Graves' disease.[o]

[m] Defined as suppressed TSH that may be: a) subclinical if free T4 normal, or b) clinical if high free T4. The majority of suppressed TSH (<0.01) are due to transient or progressive painless thyroiditis. Most patients with thyrotoxicosis are asymptomatic. Symptoms, if present, may include palpitations, heat intolerance, restlessness or anxiety, fine tremor, and/or weight loss. Consider thyroid autoantibodies (eg, anti-thyroid peroxidase [TPO] and anti-thyroglobulin [Tg]), but correlation with checkpoint inhibitor thyroiditis remains unknown.

[n] Thyrotoxicosis in this setting is usually from a destructive process, and thus anti-thyroid drugs (eg, methimazole, propylthiouracil) are not recommended. ICI-induced thyrotoxicosis usually evolves into hypothyroidism and requires replacement therapy, but sometimes resolves to normal with long-term follow-up.

[o] Usual duration of thyrotoxicosis from checkpoint immunotherapy is 4–6 weeks. Graves' disease evaluation with TSH receptor antibody (TRAb) or thyroid-stimulating immunoglobulin (TSI) measurement or thyroid uptake scan can be considered in patients with persistent thyrotoxicosis. Recommend referral to endocrinology.

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ENDOCRINE ADVERSE EVENT(S)	ASSESSMENT	MANAGEMENT
Hypophysitis[p] →	• Evaluate for symptoms[p,q] • Cortisol and ACTH (morning preferred), TSH, free T4, serum Na • Consider LH, FSH, IGF1, Prolactin, and sex hormones as appropriate • Cosyntropin stimulation testing is not recommended in acute settings[q] • Brain MRI ± contrast with pituitary/sellar cuts, especially if mass effect symptoms or concern for metastatic disease[p,r]	→ • Endocrine consultation • Hold immunotherapy until acute symptoms resolve and hormone replacement is initiated[i] • If severe symptoms with concern for mass effect, may consider high-dose steroids[s] • Treat with physiologic hormone replacement[t,u,v] • Secondary adrenal insufficiency (low ACTH, low cortisol) ▸ Physiologic steroids in ambulatory patients and stress dosing for acute illness or surgery/procedures[t] • Central hypothyroidism (normal or low TSH, low free T4) ▸ Thyroid hormone replacement, titrate to free T4 level[u]
Primary adrenal insufficiency (high ACTH with low morning cortisol, abnormal cosyntropin stimulation test) →	• Rare diagnosis that is not usually associated with checkpoint immunotherapy • If there is concern for this diagnosis, recommend endocrine consultation	

Footnotes on ICI_ENDO-4A

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FOOTNOTES

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

[p] Hypophysitis typically presents with acute or subacute symptoms from pituitary hormone loss notably adrenal insufficiency including dizziness, nausea/emesis, anorexia, severe fatigue, confusion, lethargy, and/or low blood pressure. Labs show low serum ACTH and cortisol, and sometimes low serum sodium or abnormalities of other pituitary hormones. Some patients present with symptoms from mass effect of pituitary enlargement (eg, headache, vision change), more often with anti-CTLA-4 therapies.

[q] Cosyntropin stimulation testing can be normal in acute secondary adrenal insufficiency and would not exclude hypophysitis.

[r] Hypophysitis from anti-PD-1/PD-L1 therapy may not show classic pituitary enlargement and enhancement on MRI as seen with anti-CTLA-4–associated hypophysitis. Consider imaging if diabetes insipidus present as rarely seen in isolated ICI-hypophysitis.

[s] If concern for optic chiasm compression or mass effect from hypophysitis, may consider high-dose steroids (eg, IV methylprednisolone 1 mg/ kg/day) as indicated until symptoms resolve (1–2 weeks) then rapid taper to physiologic replacement. High-dose steroids do not reverse the likelihood of permanent hormone deficit and if prolonged, may have negative impact on outcomes.

[t] Preferred treatment for adrenal insufficiency is with hydrocortisone, dosed at 20 mg PO every AM and 10 mg PO in the early afternoon for ambulatory patients. Dosing for physiologic replacement is considered higher in patients on immunotherapy due to underlying inflammation. Further titration is best guided by an endocrinologist. Once daily prednisone at an equivalent dose is an alternative regimen. Acutely symptomatic or hospitalized patients or patients undergoing surgery with general anesthesia require stress dose steroids (hydrocortisone 100 mg IV x1, then 50 mg every 8 hours, tapered based on clinical parameters) and endocrinology consultation. Patients should double their dose for 3 days for mild illness or fever in the outpatient setting. Patients typically require cortisol replacement indefinitely.

[u] See Overt hypothyroidism on ICI_ENDO-2 for levothyroxine dosing.

[v] For central hypogonadism (low LH, low FSH, and low sex hormone, not due to underlying illness) may consider testosterone supplementation in individuals and estrogen in premenopausal individuals if not otherwise contraindicated.

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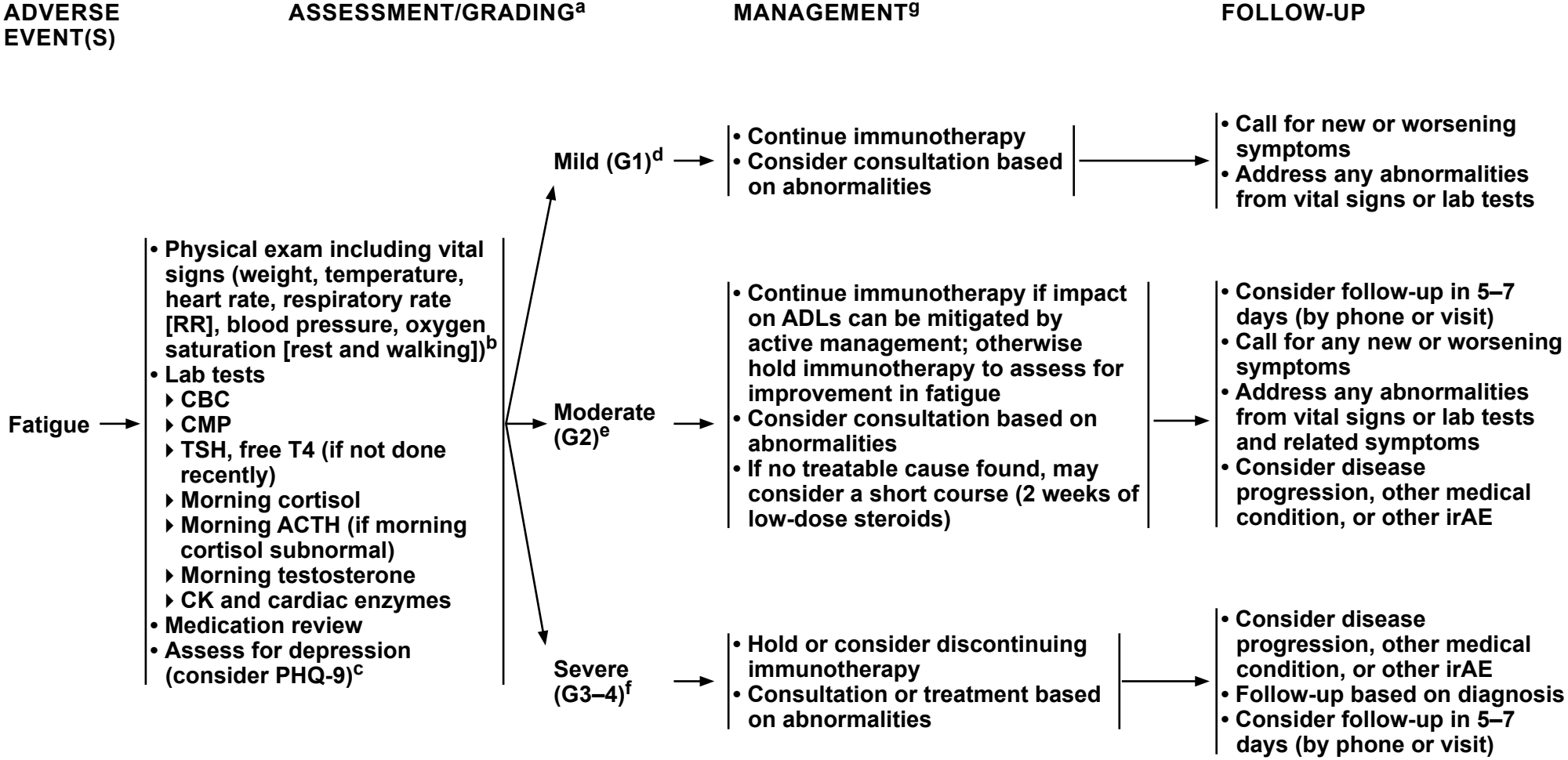

[a] If diagnostic studies indicate central hypothyroidism and/or central/secondary adrenal sufficiency (ICI_ENDO-4), see respective pages for treatment recommendations.
[b] Fatigue can be multifactorial. Other etiologies could be myositis, or pneumonitis; consider further workup.
[c] See NCCN Guidelines for Distress Management.
[d] Relieved by rest.
[e] Not relieved by rest; limiting ADLs.
[f] Not relieved by rest; limiting self care.
[g] Based on physical signs and lab tests, 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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GASTROINTESTINAL ADVERSE EVENT(S)

- Diarrhea
- Colitis[a]

ASSESSMENT/GRADING

Mild (G1)[d] →
- Consider stool evaluation to rule out infectious etiology[b]
  - *C. difficile*
  - Nucleic acid amplification tests (NAATs) for GI pathogens (other bacteria, viruses)
  - In appropriate clinical context, consider ova & parasites; molecular testing for *Giardia* and *Cryptosporidium* spp and *E. histolytica*; and microsporidia and Cyclo*spora/isospora* spp
- Based on institutional availability, consider fecal lactoferrin/calprotectin[c]

Moderate (G2)[e] → ICI_GI-2

Severe (G3–4)[f] → ICI_GI-3

MANAGEMENT[g]

- Consider holding immunotherapy[h]
- Consider loperamide or diphenoxylate/atropine for 2–3 days as an adjunct for symptom relief
  - If no improvement and not already done, obtain lab tests for infectious workup
  - Caution is warranted to avoid masking symptoms; discontinue antidiarrheals if diarrhea persists, to assess response to immunosuppressive therapy
- Hydration
- Close monitoring[i]
- If persistent or progressive symptoms, check lactoferrin/calprotectin
  - If positive, treat as G2
  - If negative and no infection, continue G1 management and consider adding mesalamine and/or cholestyramine as needed
- Dietary modifications[j]

[a] Symptoms include: watery diarrhea, cramping, urgency, abdominal pain, blood and mucus in the stool, fever, and 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 PUD and malignant bleeding.
[b] It is not necessary to wait for test results before providing therapy to manage irAEs.
[c] Consider endoscopy exam within 2 weeks if either lactoferrin or calprotectin is positive. Serial monitoring of calprotectin levels while on treatment (every 2 months) may be helpful to guide treatment duration until achieving endoscopic remission.
[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, interference with ADLs, hemodynamic instability, hospitalization, serious complications (eg, ischemic bowel, perforation, toxic mega-colon), or other colitis-related life-threatening conditions.
[g] Principles of Immunosuppression (IMMUNO-A).
[h] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[i] Eg, stool frequency, consistency, blood in stool, nocturnal symptoms, weight trend. If progressive, consider stool evaluation to rule out infectious etiology.
[j] Consider lactose-free, low-fiber diet until diarrhea subsides. Consider BRAT (bananas, rice, apple sauce, toast) diet.

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GASTROINTESTINAL ADVERSE EVENT(S)

- Diarrhea
- Colitis[a]

Moderate (G2)[e]

ASSESSMENT/GRADING

- Stool evaluation to rule out infectious etiology[b]
  - *C. difficile*
  - NAATs for GI pathogens (other bacteria, viruses)
  - In appropriate clinical context, consider ova & parasites; molecular testing for *Giardia* and *Cryptosporidium* spp and *E. histolytica*; and microsporidia and Cyclospora/isospora spp
- Based on institutional availability, consider fecal lactoferrin/calprotectin[c]
- Consider abdominal/pelvic CT with contrast[l]
- Consider GI consultation
  - Colonoscopy or flexible sigmoidoscopy ± esophagogastroduodenoscopy (EGD) with biopsy[c]

MANAGEMENT[g,q]

- Hold immunotherapy[h]
- For pathologically confirmed microscopic colitis, consider budesonide 9 mg daily prior to systemic steroids[m]
- Prednisone/IV methylprednisolone[k,n] (1–2 mg/kg/day)[o]
- If no response to oral steroids after 3 days, consider IV steroids, consider adding infliximab[p,r,s] or vedolizumab[p,r,t]
  - Consider tofacitinib or ustekinumab for infliximab- and/or vedolizumab-refractory colitis[u]

[a] Symptoms include: watery diarrhea, cramping, urgency, abdominal pain, blood and mucus in the stool, fever, and 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 PUD and malignant bleeding.
[b] It is not necessary to wait for test results before providing therapy to manage irAEs.
[c] Consider endoscopy exam within 2 weeks if either lactoferrin or calprotectin is positive. Serial monitoring of calprotectin levels while on treatment (every 2 months) may be helpful to guide treatment duration until achieving endoscopic remission.
[e] 4–6 bowel movements above baseline per day, colitis symptoms, not interfering with ADLs.
[g] Principles of Immunosuppression (IMMUNO-A).
[h] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[k] IV steroid is preferred due to possible absorption impairment.
[l] In cases with high suspicion for complications (eg, toxic megacolon, abscess, or perforation).
[m] Hughes MS, et al. J Immunother Cancer 2019;7:292.
[n] Convert to prednisone when appropriate.
[o] Treat until symptoms improve to Grade ≤1, then taper over <4 to 6 weeks. In cases where infliximab or vedolizumab is used, an attempt to taper steroids in <2 to 4 weeks should be made to minimize the complication of infection. If strong clinical suspicion for ICI diarrhea, start empiric IV steroids while waiting for EGD/colonoscopy/flexible sigmoidoscopy results.
[p] Duration of therapy with infliximab or vedolizumab is not clearly defined; however, receipt of three or more doses (at weeks 0, 2, and 6) has been associated with favorable overall survival. Repeat endoscopy and/or fecal calprotectin to assess endoscopic healing may be helpful to guide colitis treatment duration, but is optional. Principles of Immunosuppression (IMMUNO-A).
[q] An FDA-approved biosimilar for infliximab or ustekinumab is an appropriate substitute.
[r] Perform infectious disease screening (HIV; hepatitis A, B, C) and TB blood test (eg, T-Spot/QuantiFERON TB gold) (depending on facility), preferably before administering first dose of infliximab or vedolizumab. In urgent situations, treatment does not need to be held for results.
[s] Infliximab antibody testing is generally not recommended and should not delay switch of therapy.
[t] Zou F, et al. J Immunother Cancer 2021;9:e003277.
[u] Esfahani K, et al. N Engl J Med 2020;382;2374-2375; Thomas AS, et al. N Engl J Med 2021;384:581-583; Bishu S, et al. Gastroenterology 2021;160:932-934; Shirwaikar Thomas A, et al. Am J Gastroenterol 2023;118:1679-1683.

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GRADING	ASSESSMENT/GRADING	MANAGEMENT[g,q]
• Diarrhea • Colitis Severe (G3–4)[f]	• Stool evaluation to rule out infectious etiology[b] ▸ *C. difficile* ▸ NAATs for GI pathogens (other bacteria, viruses) ▸ In appropriate clinical context, consider ova & parasites; molecular testing for *Giardia* and *Cryptosporidium* spp and *E. histolytica*; and microsporidia and *Cyclospora/isospora* spp • Based on institutional availability, consider fecal lactoferrin/calprotectin[c] • Consider abdominal/pelvic CT with contrast[l] • Recommend GI consultation ▸ Colonoscopy or flexible sigmoidoscopy ± EGD with biopsy[c]	• G3: If using combination IO therapy, discontinue current therapy; consider resuming anti-PD-1/PD-L1 monotherapy after resolution of toxicity[h] • G4: Discontinue immunotherapy agent responsible for toxicity[h] • Consider inpatient care for provision of supportive care • IV methylprednisolone[n] (1–2 mg/kg/day)[o] ▸ If no response in 1–2 days or unable to transition to oral steroids, additional immunosuppression required. Continue steroids and strongly consider adding infliximab[p,r,s] or vedolizumab[p,r,t,u,v] ◊ Consider tofacitinib or ustekinumab for infliximab- and/or vedolizumab-refractory colitis[u]

[b] It is not necessary to wait for test results before providing therapy to manage irAEs.
[c] Consider endoscopy exam within 2 weeks if either lactoferrin or calprotectin is positive. Serial monitoring of calprotectin levels while on treatment (every 2 months) may be helpful to guide treatment duration until achieving endoscopic remission.
[f] More than 6 bowel movements above baseline per day, colitis symptoms, interference with ADLs, hemodynamic instability, hospitalization, serious complications (eg, ischemic bowel, perforation, toxic mega-colon), or other colitis-related life-threatening conditions.
[g] Principles of Immunosuppression (IMMUNO-A).
[h] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[l] In cases with high suspicion for complications (eg, toxic megacolon, abscess, or perforation).
[n] Convert to prednisone when appropriate.
[o] Treat until symptoms improve to Grade ≤1, then taper over <4 to 6 weeks. In cases where infliximab or vedolizumab is used, an attempt to taper steroids in <2 to 4 weeks should be made to minimize the complication of infection. If strong clinical suspicion for ICI diarrhea, start empiric IV steroids while waiting for EGD/colonoscopy/flexible sigmoidoscopy results.
[p] Duration of therapy with infliximab or vedolizumab is not clearly defined; however, receipt of three or more doses (at weeks 0, 2, and 6) has been associated with favorable overall survival. Repeat endoscopy and/or fecal calprotectin to assess endoscopic healing may be helpful to guide colitis treatment duration, but is optional. Principles of Immunosuppression (IMMUNO-A).
[q] An FDA-approved biosimilar for infliximab or ustekinumab is an appropriate substitute.
[r] Perform infectious disease screening (HIV; hepatitis A, B, C), and TB blood test (eg, T-Spot/QuantiFERON TB gold) (depending on facility), preferably before administering first dose of infliximab or vedolizumab. In urgent situations, treatment does not need to be held for results.
[s] Infliximab antibody testing is generally not recommended and should not delay switch of therapy.
[t] Zou F, et al. J Immunother Cancer 2021;9:e003277.
[u] Esfahani K, et al. N Engl J Med 2020;382;2374-2375; Thomas AS, et al. N Engl J Med 2021;384:581-583. Bishu S, et al. Gastroenterology 2021;160:932-934; Shirwaikar Thomas A, et al. Am J Gastroenterol 2023;118:1679-1683.
[v] Fecal transplantation may be considered for immunosuppressant-refractory colitis based on institutional availability and expertise.

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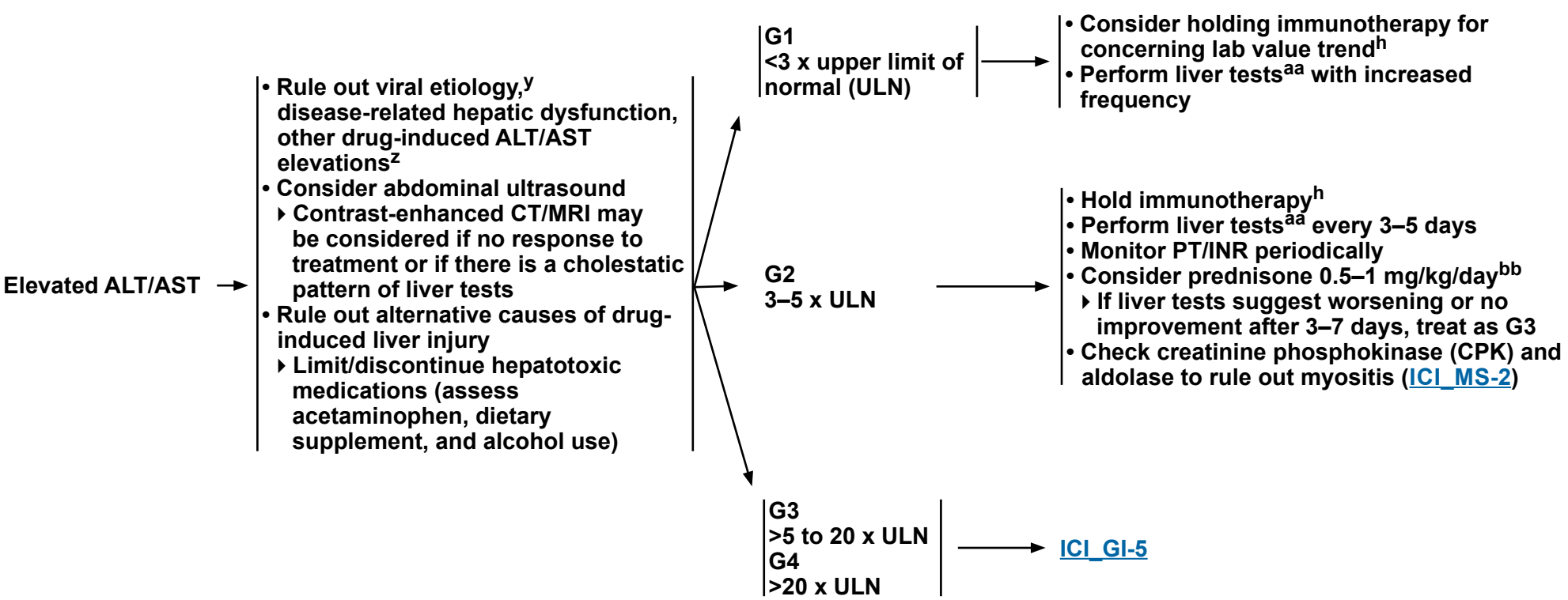

[g] Principles of Immunosuppression (IMMUNO-A).
[h] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[w] Consider initiating steroids while waiting for results in cases of G4 ALT/AST elevations.
[x] Hyperbilirubinemia of hepatic origin is generally of conjugated predominance (or conjugated hyperbilirubinemia).
[y] Consider testing for viral infections based on liver test pattern, viral risk factors, and clinical presentation including HBsAg.
[z] ANAs and anti-smooth cell antigens (ASMAs) may inform risk of irAEs and response to immunosuppression.
[aa] ALT, AST, alkaline phosphatase, bilirubin (total and direct), and albumin.
[bb] When liver tests 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.

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HEPATOBILIARY ADVERSE EVENT(S)

- Elevated ALT/AST
  - G3
    >5 to 20 x ULN
  - G4
    >20 x ULN
- Concomitant elevated bilirubin increases risk of hepatic failure (unless Gilbert syndrome)

ASSESSMENT/GRADING[w,x]

- See Assessment on ICI_GI-4
- Recommend GI/hepatology evaluation
- Synthetic LFTs
  - PT/INR, bilirubin, and serum albumin levels[x]

MANAGEMENT[g,cc]

General (G3 or G4)

- Consider diagnostic parenchymal liver biopsy if no contraindications
  - Reserve for atypical (cholestatic) clinical/biochemical presentation or when there is no response to standard therapy
- Monitor PT/INR periodically

G3

- Hold immunotherapy[h]
- Initiate prednisone/IV methylprednisolone 1 mg/kg/day[bb]
  - If no improvement after 1–2 days, consider adding steroid-sparing immunosuppressive therapy[dd,ee,ff]
- Consider inpatient care, particularly if synthetic hepatic dysfunction is observed
- Perform liver tests[aa] every 1–5 days depending on magnitude and rate of change

G4

- Discontinue immunotherapy[h]
- Initiate prednisone/IV methylprednisolone 1 mg/kg/day[bb,gg]
  - If no improvement after 1–2 days, consider adding steroid-sparing immunosuppressive therapy[dd,ee,ff]
- Inpatient care, particularly if synthetic hepatic dysfunction is observed
- Perform liver tests[aa] every 1–3 days

Footnotes on ICI_GI-5A

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FOOTNOTES

[g] Principles of Immunosuppression (IMMUNO-A).
[h] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[w] Consider initiating steroids while waiting for results in cases of G4 ALT/AST elevations.
[x] Hyperbilirubinemia of hepatic origin is generally of conjugated predominance (or conjugated hyperbilirubinemia).
[aa] ALT, AST, alkaline phosphatase, bilirubin (total and direct), and albumin.
[bb] When liver tests 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.
[cc] Infliximab has been associated with drug-induced liver injury, particularly drug-induced autoimmune hepatitis.
[dd] Mycophenolate mofetil treatment (up to 1.5 g every 12 hours) can be considered. Tacrolimus can be considered over mycophenolate in patients with concomitant diarrhea or leukopenia. Tacrolimus can be added to mycophenolate in refractory cases. When tacrolimus is used, renal function should be monitored. Check a single tacrolimus trough level 2 to 3 days after starting tacrolimus and if the dose is increased. There is no target tacrolimus trough level; target the lowest dose that induces a biochemical response. Taper serially, starting with medications with the highest toxicity first (typically prednisone).
[ee] Response to steroid-sparing immunosuppressive therapy (eg, in alphabetical order: ATG, azathioprine, mycophenolate, tacrolimus, tocilizumab) may be delayed and may require prolonged therapy (≥1 week) in the treatment of irAEs.
[ff] Due to an increased risk of GI perforation with IL-6 inhibitors (tocilizumab), assess for history of clinically active diverticular disease prior to initiating therapy and use with caution in those patients.
[gg] Consider early concomitant use of mycophenolate with the initiation of steroids.

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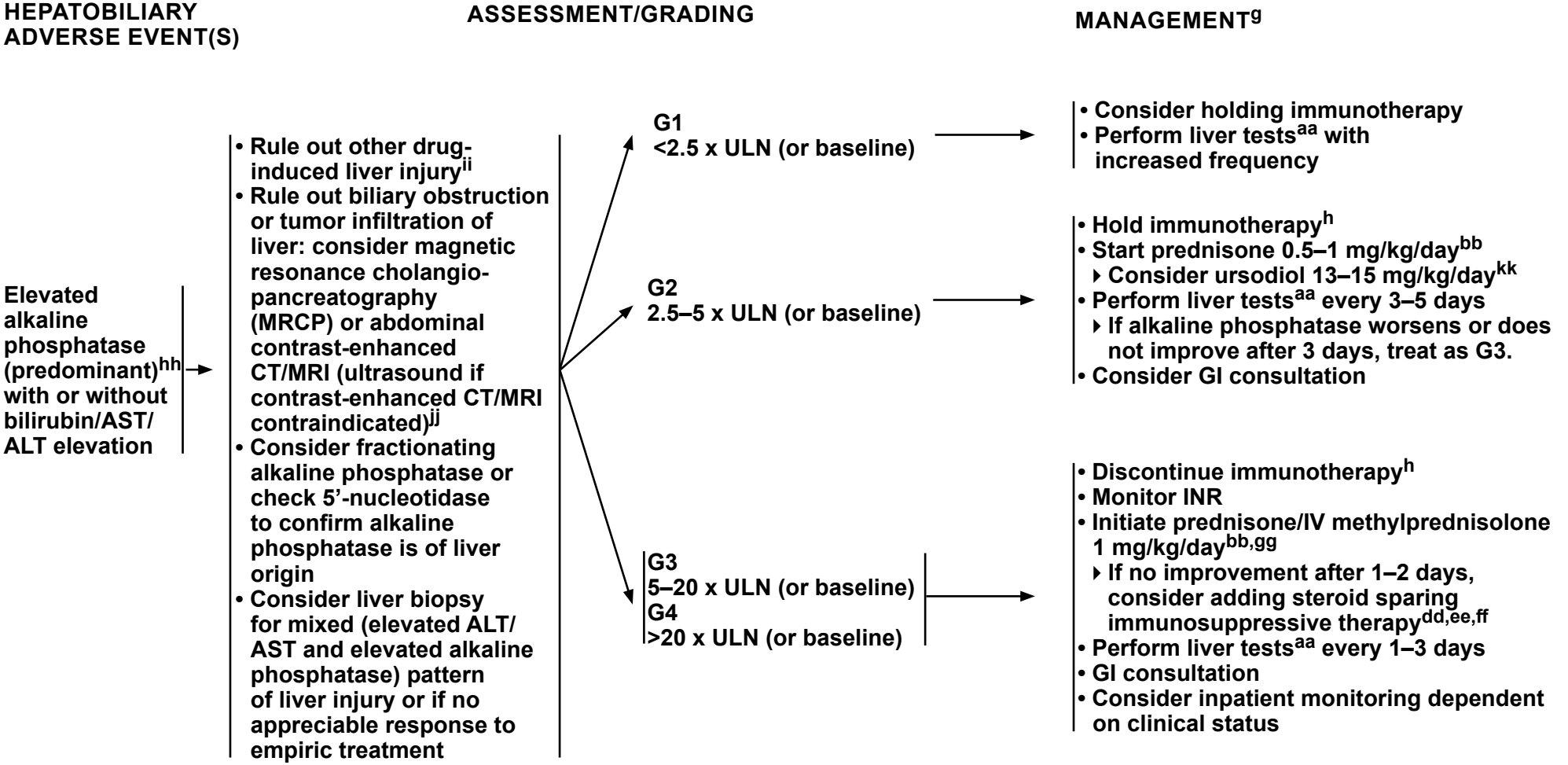

Footnotes on ICI_GI-6A

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FOOTNOTES

[g] Principles of Immunosuppression (IMMUNO-A).
[h] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[aa] ALT, AST, alkaline phosphatase, bilirubin (total and direct) and albumin.
[bb] When liver tests 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.
[dd] Mycophenolate mofetil treatment (up to 1.5 g every 12 hours) can be considered. Tacrolimus can be considered over mycophenolate in patients with concomitant diarrhea or leukopenia. Tacrolimus can be added to mycophenolate in refractory cases. When tacrolimus is used, renal function should be monitored and tacrolimus trough levels should be checked ~2 to 3 days if dose increased. There is no target tacrolimus trough level; target the lowest dose that induces a biochemical response. Taper serially, starting with medications with the highest toxicity first (typically prednisone).
[ee] Response to steroid-sparing immunosuppressive therapy (eg, in alphabetical order: ATG, azathioprine, mycophenolate, tacrolimus, tocilizumab) may be delayed and may require prolonged therapy (≥1 week) in the treatment of irAEs.
[ff] Due to an increased risk of GI perforation with IL-6 inhibitors (tocilizumab), assess for history of clinically active diverticular disease prior to initiating therapy and use with caution in those patients.
[gg] Consider early concomitant use of mycophenolate with the initiation of steroids.
[hh] There is no predetermined alkaline phosphatase elevation. Alkaline phosphatase ≥ 3X ULN with/without AST/ALT 1–2X ULN is highly suggestive of cholangitis.
[ii] Drug-induced cholestasis may include penicillins, trimethoprim-sulfamethoxazole (TMP-SMZ), macrolides, tetracycline, antifungals, antiretrovirals, anti-inflammatory and psychotropes.
[jj] Endoscopic retrograde cholangiopancreatography (ERCP) can be considered.
[kk] Ursodiol can be administered as a single daily dose. Split dosing (BID or TID) can be considered if patient experiences side-effects such as diarrhea.

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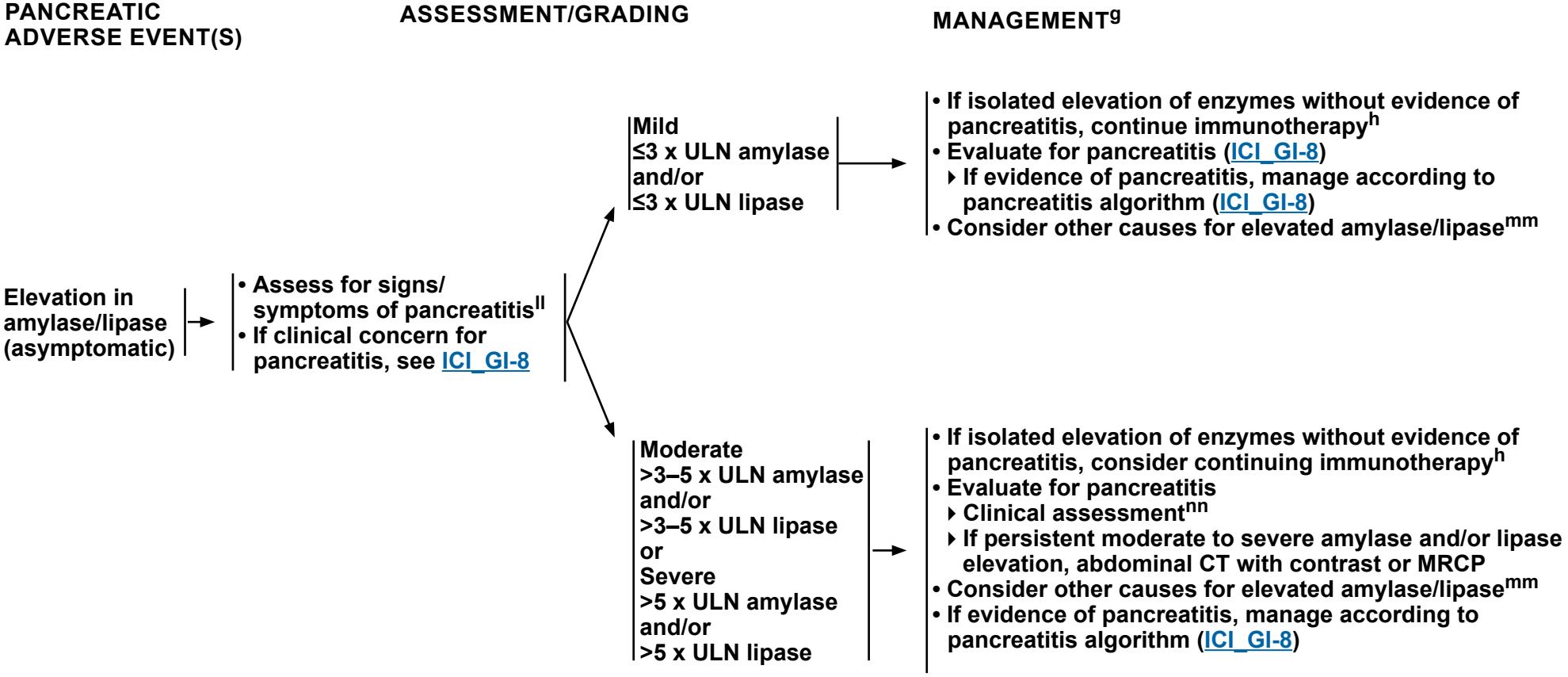

[g] Principles of Immunosuppression (IMMUNO-A).
[h] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[ll] Mild symptoms of pancreatitis can include: nausea, bloating, belching, abdominal pain, or back pain.
[mm] Inflammatory bowel disease, irritable bowel syndrome, bowel obstruction, gastroparesis, nausea/vomiting, medications, alcohol, and/or DM.
[nn] 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).

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PANCREATIC[oo] ADVERSE EVENT(S)

ASSESSMENT/GRADING

MANAGEMENT[g,tt]

Acute pancreatitis[pp]

- Assess for signs/symptoms of pancreatitis
- Abdominal CT with contrast
- Consider MRCP if clinical suspicion of pancreatitis and no radiologic evidence on CT
- Assess for other causes (ie, alcohol use, biliary)

Mild (G2)[qq]

- Consider holding immunotherapy[h]
- Consider gastroenterology referral
- Consider IV hydration
- Manage as per elevation in amylase/lipase (asymptomatic) (ICI_GI-6)

Moderate (G3)[rr]

- Hold immunotherapy[h]
- Gastroenterology referral
- IV hydration
- Prednisone/IV methylprednisolone 0.5–1 mg/kg/day[uu]

Severe (G4)[ss]

- Permanently discontinue immunotherapy[h]
- Gastroenterology referral
- IV hydration
- Prednisone/IV methylprednisolone 1–2 mg/kg/day[uu]

[g] Principles of Immunosuppression (IMMUNO-A).
[h] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[oo] No requirement for routine monitoring of potential pancreatitis with imaging.
[pp] 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.
[qq] Asymptomatic amylase/lipase elevation OR radiologic features on CT or clinical findings concerning for pancreatitis. The decision to hold immunotherapy is based on clinical suspicion. If amylase/lipase >3 x ULN or CT findings are prominent, holding immunotherapy is recommended.
[rr] Symptomatic pain or vomiting AND any amylase/lipase elevation or CT findings suggesting pancreatitis.
[ss] Features of pancreatitis (enzyme elevation OR CT findings) with life-threatening consequences OR hemodynamic instability OR urgent intervention indicated.
[tt] Evaluate for signs/symptoms of pancreatic exocrine insufficiency and/or DM, and supplement if needed. Follow-up over time to monitor for pancreatic insufficiency.
[uu] Treat until symptoms improve to Grade ≤1, then taper over 4–6 weeks.

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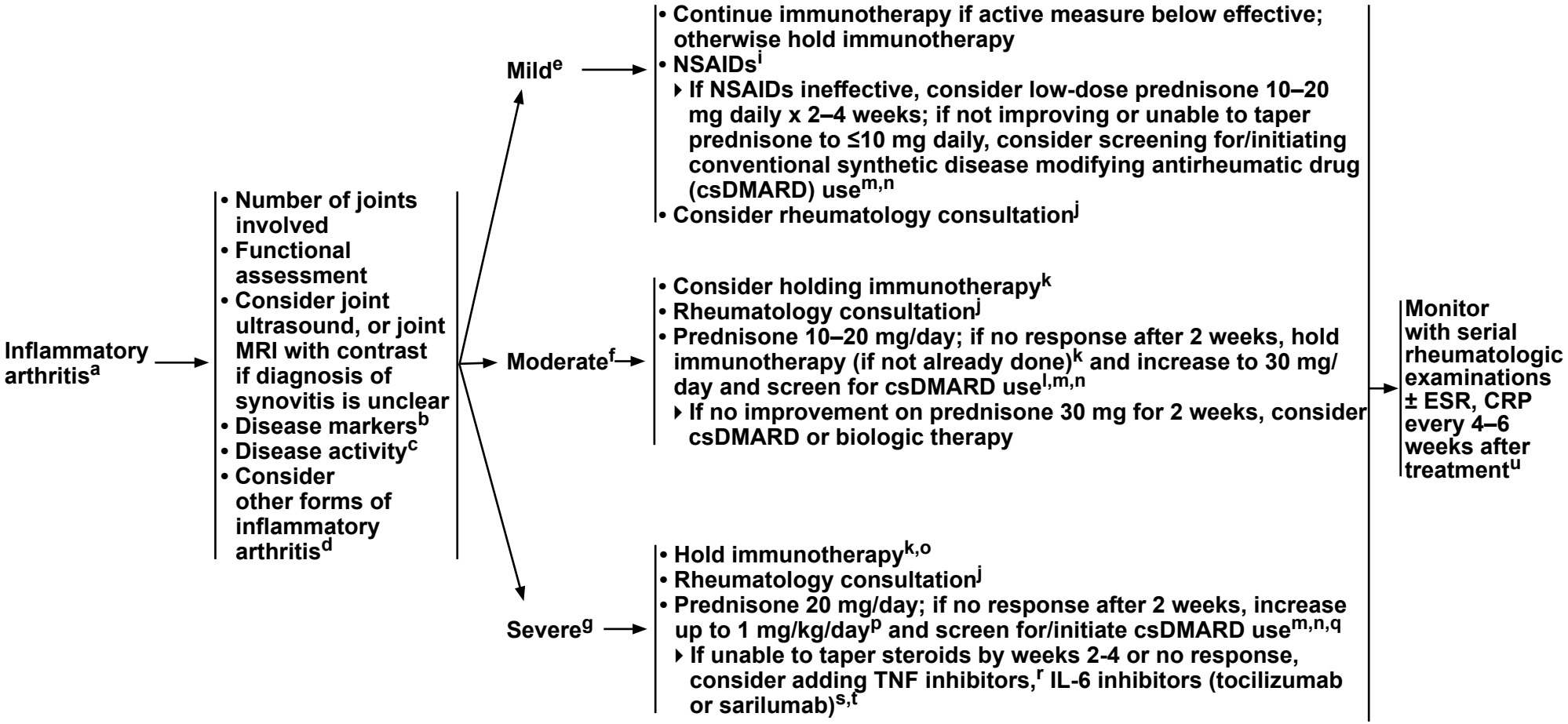
MUSCULOSKELETAL ADVERSE EVENT(S)

ASSESSMENT/GRADING

MANAGEMENT[h]



Footnotes on ICI_MS-1A

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FOOTNOTES

[a] Clinical symptoms: joint pain, joint swelling; inflammatory symptoms: morning stiffness, stiffness after inactivity, improvement in stiffness with activity.
[b] Anticyclic citrullinated peptide (anti-CCP) and rheumatoid factor (RF).
[c] CRP and ESR.
[d] Such as gout, infection.
[e] Mild in severity; only 1 or 2 joints involved. Consider aspiration to rule out septic joint if infection is suspected.
[f] At least one joint with severe inflammation.
[g] Limits ADLs, several joints involved.
[h] Principles of Immunosuppression (IMMUNO-A).
[i] Consider other non-opioid medications (eg, COX2 inhibitors or gabapentin/pregabalin).
[j] Consider intra-articular steroids in affected joint(s), depending on joint location and number involved and joint aspiration and fluid analysis.
[k] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[l] If improving after 2-4 weeks, begin prednisone taper by 5 mg/week.
[m] Screen for csDMARD use with hepatitis serologies, CBC, TB, and LFTs.
[n] csDMARDs include methotrexate (with folic acid to reduce side effects), sulfasalazine, leflunomide, or hydroxychloroquine which can be used alone or in combination pending symptom response.
[o] 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.
[p] Treat until symptoms improve to Grade ≤1, then taper over 4–6 weeks.
[q] If patients need to be on steroids long-term, see IMMUNO-A.
[r] TNF inhibitors include etanercept, adalimumab, infliximab, golimumab or certolizumab (FDA-approved biosimilars as appropriate). There is a slight increased risk of relapse.
[s] Due to an increased risk of GI perforation with IL-6 inhibitors (tocilizumab or sarilumab), screen for diverticular disease prior to initiating therapy and use with caution in patients with clinically active diverticular disease.
[t] An FDA-approved biosimilar is an appropriate substitute for tocilizumab.
[u] Consider ESR and CRP to monitor response if elevated at the onset of therapy. Inflammatory arthritis may become a chronic process requiring long-term management.

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MUSCULOSKELETAL ADVERSE EVENT(S)

Myositis[v] (proximal muscle weakness, neck flexor weakness, with or without myalgias)

ASSESSMENT/GRADING

- Evaluate for concomitant irAEs myasthenia gravis and myocarditis, as myositis can exist as an overlap syndrome[w]
- Urgent evaluation is essential with labs and clinical team
- CK, aldolase, and troponin I or T levels, CMP (AST/ALT may be elevated in myositis), ECG (compare to baseline if possible)
- Muscle strength testing (proximal muscles, including neck flexors, and distal muscles)
- Consider MRI without contrast, EMG, muscle biopsy and myositis antibodies if clinically indicated

MANAGEMENT[h]

Mild[x] or Moderate[y]

- Consider holding or discontinuing immunotherapy[k,aa]
- Prednisone 0.5–1 mg/kg[bb,cc]
- Monitor serial CK/aldolase[dd]
- If no response to therapy, consider re-evaluating for myasthenia gravis (ICI_NEURO-1) and myocarditis (ICI_CARDIO-1), and escalate to management for severe or life-threatening myositis[ee]

Severe or Life-threatening[z]

- Hold immunotherapy; consider discontinuing for select patients[k]
- Inpatient care for severe or life-threatening myositis
- Rheumatology or neurology consultation
  - Cardiology and/or neurology consultation if myocarditis and/or myasthenia gravis is involved[ee]
- Consider IV methylprednisolone 500 mg to 1 g/day x 3 days followed by prednisone 1 mg/kg/day. After 4 weeks, taper prednisone by 10 mg/month.
  - If no improvement after 2–4 weeks, consider the addition of a csDMARD[cc]
- Consider IVIG (2 g/kg administered in divided doses per package insert), mycophenolate mofetil or rituximab[ff] for significant dysphagia, life threatening situations, or cases refractory to steroids
- Abatacept with ruxolitinib has been used in concomitant myositis and myocarditis[gg]
- Monitor serial aldolase/CK until symptoms have resolved and tapered off steroids

[h] Principles of Immunosuppression (IMMUNO-A).
[k] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[v] Myositis is a disorder characterized by inflammation and/or weakness involving the skeletal muscles with elevated muscle enzymes.
[w] These concomitant irAEs can occur within the first month of therapy (median onset of 28–30 days).
[x] CPK elevation less than 1000 mcg/L, mild weakness and minimal impairment of ADLs; no myasthenia gravis and/or myocarditis co-existing with myositis.
[y] Moderate pain associated with objective weakness and/or elevation of muscle enzymes (CK or aldolase) limiting self-care ADLs.
[z] Urgent intervention is indicated.
[aa] Would not recommend holding ICI if no elevation in CPK or evidence of active myositis.
[bb] If improving after 2–4 weeks, begin slow prednisone taper by 5 mg/week. If unable to taper, or no response, add csDMARD.
[cc] Methotrexate (with folic acid) as a steroid-sparing agent to speed up taper. If contraindication to methotrexate, consider mycophenolate mofetil or azathioprine.
[dd] Do not need to trend aldolase unless aldolase elevation is the only evidence of myositis (CPK normal). Aldolase can be falsely elevated if blood sample is hemolyzed.
[ee] There have been case reports of a life-threatening triad of myositis, myocarditis, and myasthenia gravis.
[ff] An FDA-approved biosimilar is an appropriate substitute for rituximab.
[gg] Salem JE, et al. Cancer Discov 2023;13:1100-1115.

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MUSCULOSKELETAL ADVERSE EVENT(S)	ASSESSMENT/GRADING	MANAGEMENT[h]
Polymyalgia rheumatica (PMR)[hh]	• Assess for bilateral shoulder and hip girdle pain, and morning stiffness • Screen for GCA symptoms (see below) ▸ If visual symptoms or loss, see GCA Assessment/Grading and Management below • ESR and CRP	• Continue immunotherapy ▸ If vision changes or loss present, hold immunotherapy until evaluated for GCA[k] • Start prednisone 10–20 mg/day[ii] ▸ If no resolution, consider holding immunotherapy[k] and increasing prednisone to 30–40 mg[jj] ▸ If unable to taper prednisone or no improvement in symptoms, consider: ◊ csDMARDs such as methotrexate ◊ IL-6 inhibitors (tocilizumab or sarilumab)[s,t] ▸ Rheumatology consultation
Giant cell arteritis (GCA) (Visual symptoms, headache, scalp tenderness, jaw claudication, often associated with fevers, night sweats, and weight loss)	• Screen for GCA symptoms ▸ If symptoms present, initiate prednisone 1 mg/kg/day with urgent referral to vascular surgery or ophthalmology for temporal artery biopsy ± ultrasound due to risk of vision loss ▸ If available, refer to rheumatology • ESR and CRP	• Hold immunotherapy[k] • If not already started, initiate prednisone 1 mg/kg/day taper over 8–12 weeks,[jj,kk] longer taper may be required • Urgent referral to rheumatology even in mild cases for consideration of IL-6 inhibitors (tocilizumab or sarilumab)[s,t] • If visual symptoms: ▸ Consider IV methylprednisolone 500–1000 mg x 3 days, followed by prednisone 1 mg/kg, then taper[jj,kk] ▸ Urgent referral to ophthalmology or vascular surgery

[h] Principles of Immunosuppression (IMMUNO-A).
[k] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[s] Due to an increased risk of GI perforation with IL-6 inhibitors (tocilizumab or sarilumab), screen for diverticular disease prior to initiating therapy and use with caution in patients with clinically active diverticular disease.
[t] An FDA-approved biosimilar is an appropriate substitute for tocilizumab.
[hh] Pain and/or stiffness in the morning usually involving bilateral shoulders and hip girdle region that limits instrumental or self-care ADLs.
[ii] PMR requires a slow taper. If improving in 4 weeks, taper by 2.5 mg every 2–4 weeks.
[jj] PJP prophylaxis if it is anticipated that patient will be treated with >20 mg prednisone for >4 weeks.
[kk] GCA requires a slower taper. Goldstein BL, et al. Arthritis Rheumatol 2014;66:768-769; Micaily I, et al. Ann Oncol 2017;28:2621-2622; Calabrese LH, et al. Nat Rev Rheumatol 2018;14:569-579.

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NERVOUS SYSTEM ADVERSE EVENT(S)

Myasthenia gravis[a]

ASSESSMENT/GRADING

- Neurology consultation. Myasthenia gravis can occur in combination with myositis and myocarditis.
- Acetylcholine receptor (AChR) antibodies, anti–muscle-specific tyrosine kinase antibodies, and anti-striational antibodies in blood (not needed for diagnosis)
- Pulmonary function assessment with negative inspiratory force (NIF) and vital capacity (VC)
- To rule out myositis/overlap syndrome, check CPK and aldolase
- Perform cardiac exam, check ECG, test troponin, and consider transthoracic echocardiogram (TTE) for possible concomitant myocarditis
- EMG/nerve conduction study (NCS) with repetitive nerve stimulation and, if available, single fiber EMG
- Consider MRI of the brain with and without contrast to rule out metastasis/leptomeningeal disease if there is facial/ocular/bulbar weakness

MANAGEMENT[d]

Moderate (G2)[b]

- Discontinue immunotherapy[e]
- Consider inpatient care (even for initially mild cases, which can progress rapidly with a high mortality rate)
- Low-dose oral prednisone 20 mg daily.[f]
  - If no symptom improvement on low dose
    - ◊ Increase every 3–5 days to a target dose of 1 mg/kg/day but not more than 100 mg daily
    - ◊ Taper steroid based on symptom improvement
- Pyridostigmine 30 mg TID and gradually increase to maximum of 120 mg orally four times a day as tolerated and based on symptoms

Severe (G3–4)[c]

- Permanently discontinue immunotherapy[e]
- Inpatient care (may need intensive care unit [ICU]-level monitoring)
- IV methylprednisolone 1–2 mg/kg/day[f] (steroid taper based on symptom improvement)
- Initiate plasmapheresis or IVIG[g]
  - Consider adding rituximab[h] (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
- Frequent pulmonary function assessment
- Daily neurologic evaluation
- Avoid medications that can worsen myasthenia[f,i]

[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 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] Principles of Immunosuppression (IMMUNO-A).

[e] 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] An FDA-approved biosimilar is an appropriate substitute for rituximab.

[i] Examples include, but are not limited to, beta-blockers, fluoroquinolones, and IV magnesium.

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NERVOUS SYSTEM ADVERSE EVENT(S)	ASSESSMENT/GRADING	MANAGEMENT[d]
Guillain-Barré syndrome (GBS)[j] →	• Inpatient care with access to ICU-level monitoring • Neurology consultation • MRI of the spine with and without contrast (rule out compressive lesion) • Serum ganglioside antibody tests for GBS variants (GQ1b for Miller Fisher variant associated with ataxia and ophthalmoplegia) • Pulmonary function testing (NIF/VC) • EMG/NCS[k] • Lumbar puncture[l] (not needed for diagnosis) →	Moderate (G2)[m] or Severe (G3–4)[n] →	• Discontinue immunotherapy[e] • Inpatient care with capability of rapid transfer to ICU-level monitoring • Start IVIG[g] or plasmapheresis in addition to IV methylprednisolone 1 gram daily for 5 days[o] then taper over 4 weeks • Frequent neurologic evaluation and pulmonary function monitoring • Monitor for concurrent autonomic dysfunction • Gabapentin, pregabalin, or duloxetine for pain

[d] Principles of Immunosuppression (IMMUNO-A).
[e] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[g] Total dosing should be 2 g/kg, administered in divided doses per package insert.
[j] 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.
[k] Early EMG/NCS findings may assess potential severity of GBS (Sejvar JJ, et al. Vaccine 2011;29:599-612; Leonhard SE, et al. Nat Rev Neurol 2019;15:671-683) and rule out sensory ganglionopathy, which may have a different prognosis.
[l] Cerebrospinal fluid (CSF) typically has elevated protein and often elevated white blood cell (WBC) count; while cytology is negative in typical GBS, it is important to send given the risk of leptomeningeal carcinomatosis. Consider infectious disease consult. Infectious disease workup: 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 normal glucose, normal culture, and Gram stain. May see reactive lymphocytes or histiocytes on cytology.
[m] Some interference with ADLs, symptoms concerning to patient.
[n] Limiting self-care and aids warranted, weakness limiting walking, any dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms.
[o] 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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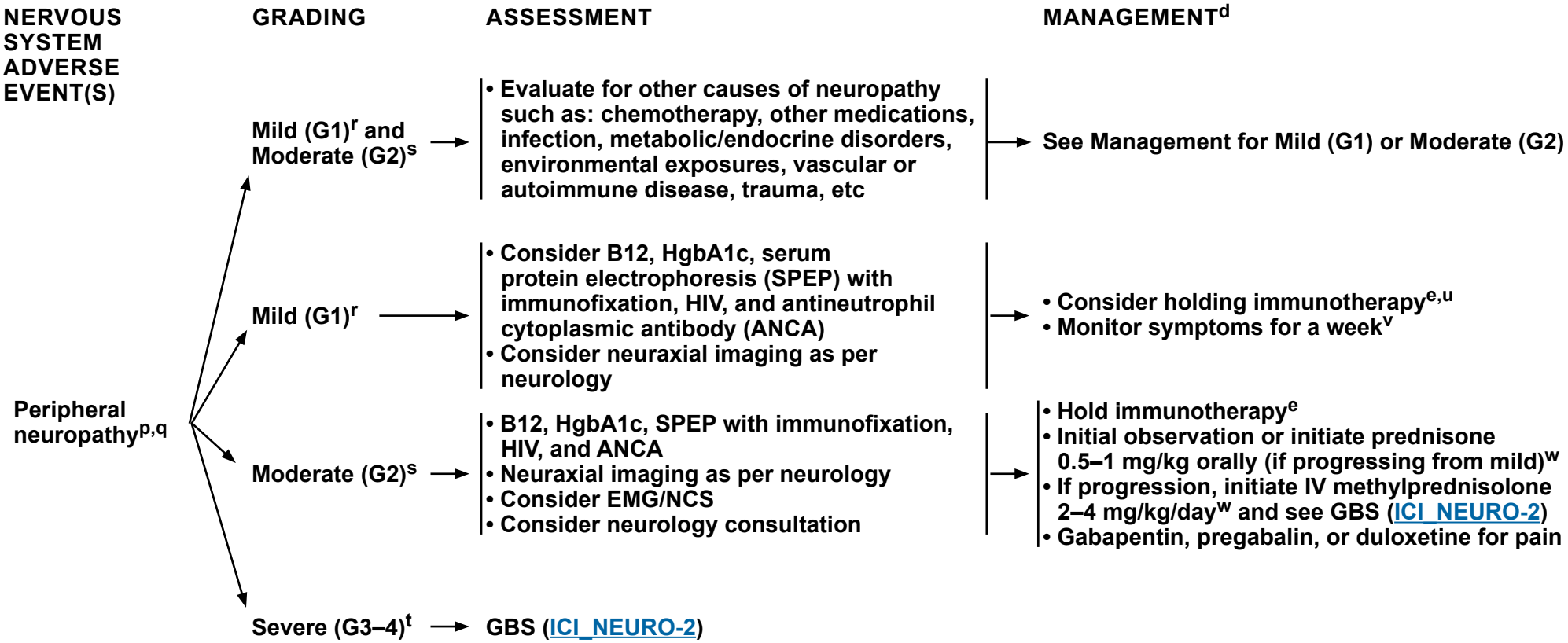

[d] Principles of Immunosuppression (IMMUNO-A).
[e] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[p] The presence of painful, asymmetric sensory/motor deficits should raise concern for mononeuritis multiplex and prompt evaluation for vasculitis or potentially life-threatening autonomic (eg, myenteric plexus) dysfunction. Hypo- or areflexia. Isolated sensory deficit or sensory plus lower motor neuron deficit.
[q] 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.
[r] No interference with function and symptoms not concerning to patient. Note: any cranial nerve problem should be managed as moderate.
[s] Some interference with ADLs, symptoms concerning to the patient (ie, pain but no weakness or gait limitation).
[t] Limiting self-care and aids warranted, weakness limiting walking or respiratory problems (ie, leg weakness, foot drop, rapidly ascending sensory changes). Severe peripheral neuropathy and sensory ganglionopathy are not necessarily GBS but the management can be similar.
[u] There is a low threshold to hold ICIs in mild cases of peripheral neuropathy.
[v] Specifically monitor for new interference with iADLs from either pain or weakness, gait difficulty, ataxia, or autonomic changes.
[w] 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[x]	• MRI of the brain with and without contrast[z] + pituitary protocol • Consider MRI of the spine with and without contrast, especially if abnormal neurologic exam of extremities, or unable to obtain exam • Lumbar puncture[aa] • Consider neurology consultation	• Hold immunotherapy[e] if mild/moderate • Consider discontinuing immunotherapy if severe • Inpatient care (G3–4[cc]) • Consider IV acyclovir[dd] until HSV and VZV PCR results obtained • Add bacterial coverage until cultures/panel results are back • Rule out bacterial and viral infection, then closely monitor off steroids or consider prednisone 0.5–1 mg/kg/day or IV methylprednisolone 1–2 mg/kg/day if moderate/severe symptoms[ee]
Encephalitis[y]	• Neurology consultation • MRI of the brain with and without contrast[bb] • Consider MRI of the spine with and without contrast, especially if abnormal neurologic exam of extremities, or unable to obtain exam • Lumbar puncture[aa] • EEG to evaluate for subclinical seizures • ESR, CRP, ANCA (if vasculitic process suspected), and thyroid panel including TPO and Tg • Autoimmune encephalopathy and paraneoplastic panel in CSF and serum	• Hold immunotherapy[e] if mild • Discontinue immunotherapy if moderate/severe • Inpatient care (G3–4[cc]) • Consider IV acyclovir[dd] until HSV and VZV PCR results are obtained • Add bacterial coverage until cultures/panel results are back • Trial of IV methylprednisolone 1–2 mg/kg/day[ee] • If severe or progressing symptoms over 24 h, strongly consider IV methylprednisolone 1 g daily for 3–5 days plus IVIG[g] or plasmapheresis • If positive for autoimmune encephalopathy antibody or limited or no improvement after 7–14 days, consider rituximab[h]

[d] Principles of Immunosuppression (IMMUNO-A).
[e] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[g] Total dosing should be 2 g/kg, administered in divided doses per package insert.
[h] An FDA-approved biosimilar is an appropriate substitute for rituximab.
[x] 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).
[y] Confusion, altered behavior, headaches, seizures, short-term memory loss, depressed level of consciousness, focal weakness, and speech abnormality
[z] May reveal leptomeningeal enhancement that can resemble leptomeningeal metastasis. CSF sampling for cytology evaluation is needed to differentiate.
[aa] Measure opening pressure and check cell count, protein glucose, Gram stain, culture, PCR for HSV, VZV, CMV, and other viral PCRs depending on suspicion, cytology, flow cytometry, and oligoclonal bands. If the patient is encephalopathic, check autoimmune encephalopathy panel. May see elevated WBC with normal glucose, normal culture, Gram stain, and elevated protein. May see reactive lymphocytes or histiocytes on cytology.
[bb] May reveal T2/FLAIR changes typical of what is seen in autoimmune encephalopathies or limbic encephalitis or may be normal.
[cc] Limiting self-care and aids warranted.
[dd] 10 mg/kg IV every 8 hours.
[ee] Taper steroids over 4 weeks once symptoms resolve.

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NERVOUS SYSTEM ADVERSE EVENT(S)	ASSESSMENT	MANAGEMENT[d]
Demyelinating disease[ff] (optic neuritis,[gg] transverse myelitis,[hh] ADEM[ii] [acute demyelinating encephalomyelitis])	• Neurology consultation • MRI of the spine and brain with and without contrast[jj] • Lumbar puncture[kk] • B12, copper, HIV, syphilis serologies, ANA, anti-Ro/La antibodies, aquaporin-4 IgG, myelin oligodendrocyte glycoprotein (MOG) IgG, autoimmune encephalopathy panel, and paraneoplastic panel • Evaluation for constipation and urinary retention with bladder scan	• Discontinue immunotherapy[e] • Inpatient care • IV methylprednisolone 1 g/day[ee] for 3–5 days • If there is no response or worsening after 48 hours on high-dose IV methylprednisolone, consider IVIG[g] or plasmapheresis

[d] Principles of Immunosuppression (IMMUNO-A).
[e] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[g] Total dosing should be 2 g/kg, administered in divided doses per package insert.
[ee] Taper steroids over 4 weeks once symptoms resolve.
[ff] Guidon AC, et al. J Immunother Cancer 2021;9:e0028890.
[gg] Vision loss, eye pain, decreased visual acuity, visual field loss, dyschromatopsia, relative afferent pupillary defect, optic disc edema.
[hh] Acute or subacute weakness or sensory changes bilaterally, often with bowel/bladder changes and spinal level to pinprick, hyperreflexia, positive Babinski.
[ii] May present with headache, confusion, seizures, depressed level of consciousness, speech abnormality, focal weakness, sensory change (numbness or tingling), ataxia/loss of balance, or vision loss.
[jj] In patients with suspected optic neuritis, MRI of the orbits with and without contrast is recommended.
[kk] Cell count, protein, glucose, oligoclonal bands, viral PCRs, flow cytometry and cytology, and paraneoplastic panel.

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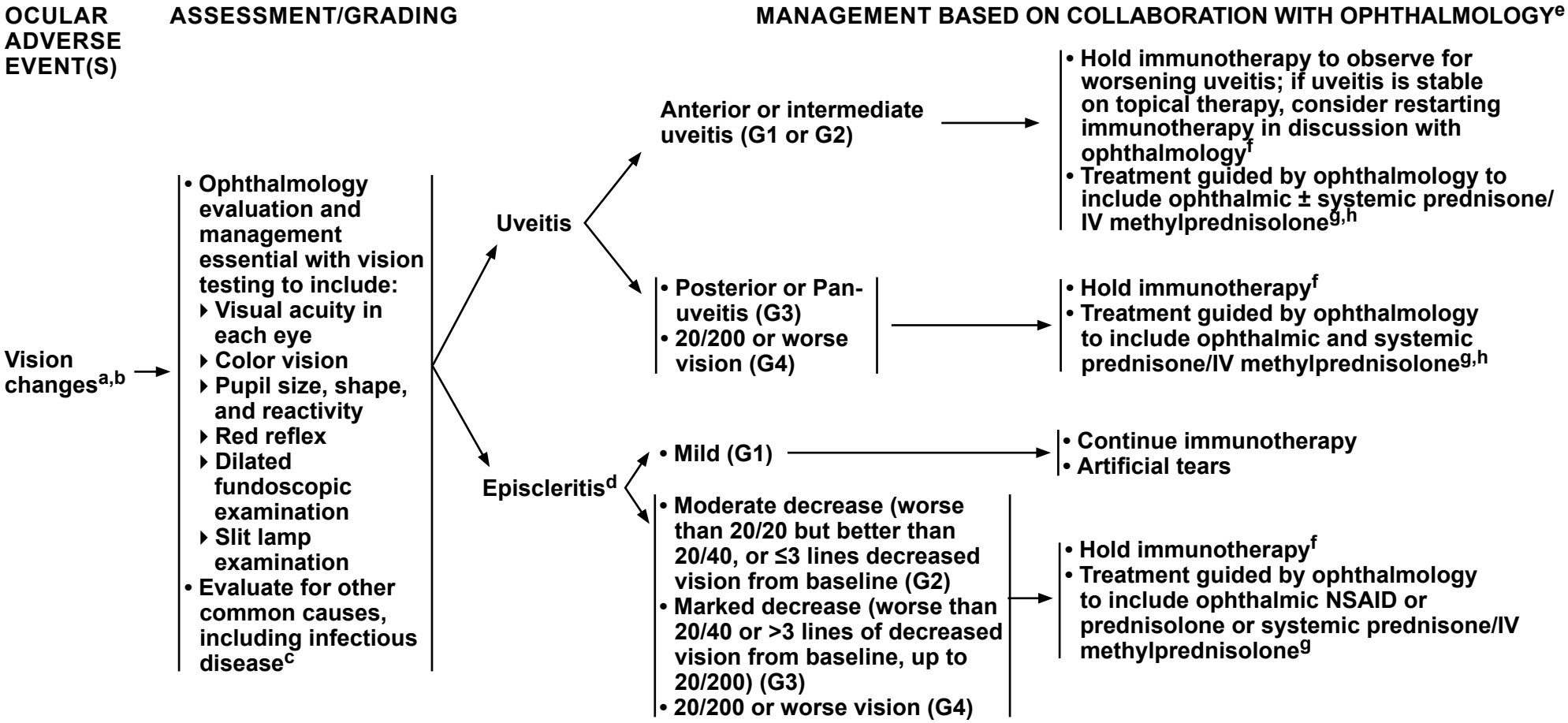

[a] Patients experiencing ocular AEs may present with any of the following symptoms: blurred/distorted vision, blind spots, change in color vision, photophobia, tenderness/pain, eyelid swelling, and proptosis. Both uveitis and episcleritis can be associated with eye redness but slit lamp examination is essential to rule out anterior chamber inflammation.

[b] See ICI_MS-3 for management of giant cell arteritis (GCA).

[c] Etiologies such as HLA-B27, syphilis, toxoplasmosis, and tuberculosis can cause uveitis and therefore should be evaluated for and ruled out prior to stopping ICI therapy and/or initiating other local therapies.

[d] Treat blepharitis per the episcleritis algorithm.

[e] Principles of Immunosuppression (IMMUNO-A).

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

[g] Treat with 1 mg/kg/day, not to exceed 60 mg/day until symptoms improve to Grade ≤1, then taper over 4–6 weeks.

[h] If refractory to high-dose systemic steroids, consider adding infliximab, FDA-approved biosimilar, or antimetabolites (eg, methotrexate) for pan-uveitis.

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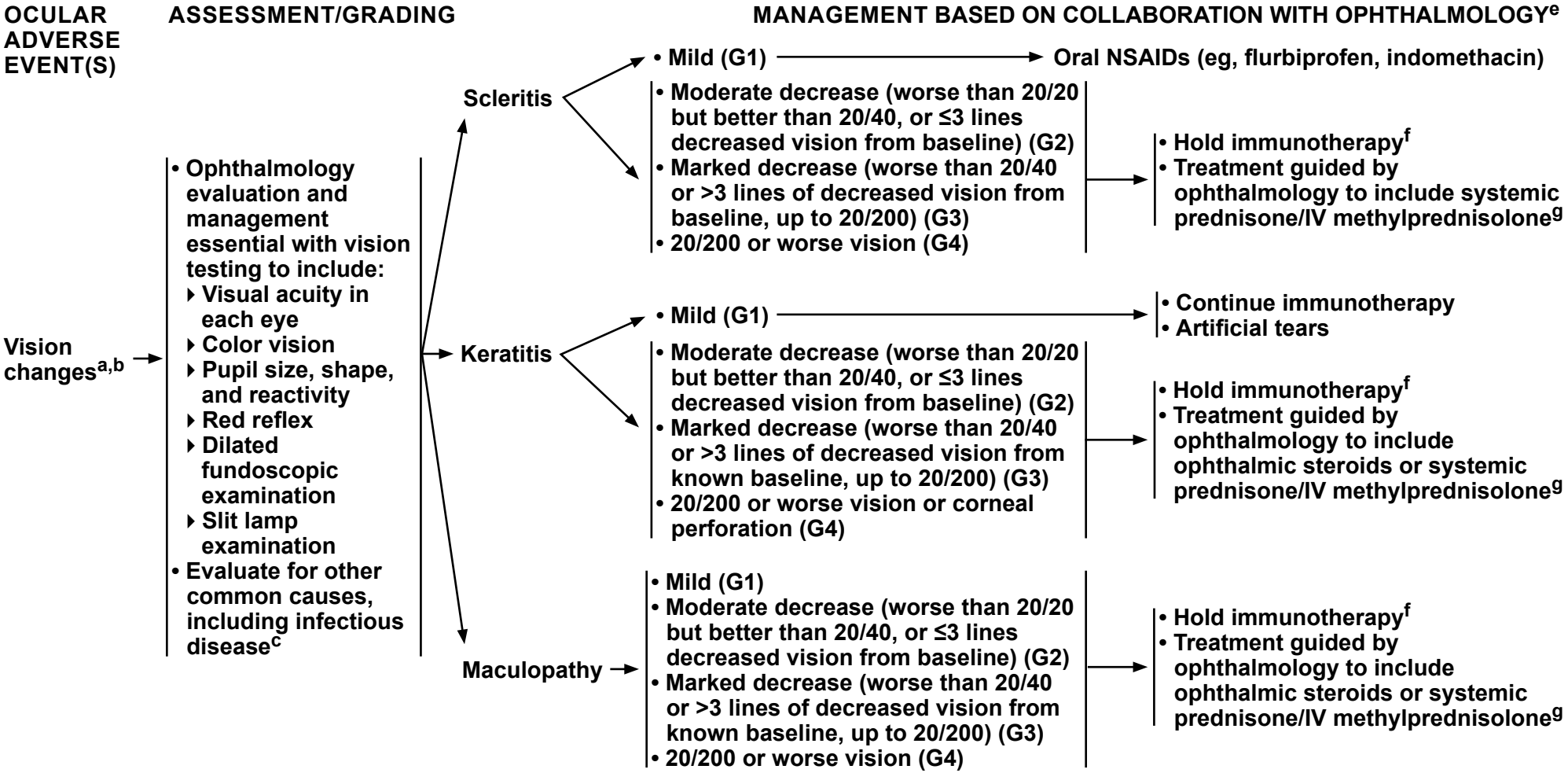

[a] Patients experiencing ocular AEs may present with any of the following symptoms: blurred/distorted vision, blind spots, change in color vision, photophobia, tenderness/pain, eyelid swelling, and proptosis. Both uveitis and episcleritis can be associated with eye redness but slit lamp examination is essential to rule out anterior chamber inflammation.
[b] See ICI_MS-3 for management of giant cell arteritis (GCA).
[c] Etiologies such as HLA-B27, syphilis, toxoplasmosis, and tuberculosis can cause uveitis and therefore should be evaluated for and ruled out prior to stopping ICI therapy and/or initiating other local therapies.
[e] Principles of Immunosuppression (IMMUNO-A).
[f] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[g] Treat with 1 mg/kg/day, not to exceed 60 mg/day until symptoms improve to Grade ≤1, then taper over 4–6 weeks.

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PULMONARY ADVERSE EVENT(S)

Pneumonitis[a]

GRADING

Mild (G1)[b] →

MANAGEMENT[f]

- Consider holding immunotherapy[g]
- Reassess in 1–2 weeks
  - H&P
  - Pulse oximetry (resting and with ambulation)
- Consider chest CT with contrast[h,i]
  - Consider repeat chest CT in 4–6 weeks or as clinically indicated if patient develops symptoms

Moderate (G2)[c,d] →

- Hold immunotherapy[g]
- Consider pulmonary consultation
- Minimally invasive evaluation
  - Consider infectious workup:
    - ◊ Nasal swab for potential viral pathogens[j]
    - ◊ Sputum culture (including bacterial, fungal, and acid-fast bacilli [AFB]), blood culture, and urine antigen test (pneumococcus, legionella)
  - Chest CT with contrast[h,i] and repeat chest CT in 3–4 weeks
- Invasive evaluation
  - Consider bronchoscopy with BAL (send for institutional immunocompromised panel[k]) and consider transbronchial lung biopsy if clinically feasible to rule out progressive malignancy or fungal infections
- Consider empiric broad-spectrum antibiotics (including coverage for atypical pathogens) if infection has not yet been fully excluded
- Prednisone/IV methylprednisolone 1–2 mg/kg/day[l]
- Monitor every 3–7 days with[m]:
  - H&P and Pulse oximetry (resting and with ambulation)
- If no improvement after 48–72 hours of steroids,[n] treat as grade 3

Severe (G3–4)[e] → ICI_PULM-2

[a] Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging). Symptoms may include dry cough, shortness of breath, fever, chest pain, and increased oxygen requirement. The imaging features of pneumonitis are known to be variable and may include ground-glass opacities, organizing pneumonia, hypersensitivity, reticulonodular changes, or a mixture of all these appearances.
[b] Asymptomatic; confined to one lobe of the lung or <25% of lung parenchyma.
[c] Presence of new/worsening symptoms.
[d] Consider cardiac etiologies.
[e] G3-severe symptoms involve all lung lobes or >50% of lung parenchyma, limiting self-care ADLs, oxygen indicated; G4–life-threatening respiratory compromise.
[f] Principles of Immunosuppression (IMMUNO-A).
[g] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[h] CT with contrast to rule out other etiologies if not contraindicated.
[i] See Pre-Therapy Assessment: Pulmonary on IMMUNO-2.
[j] Viral pathogen assessment should include COVID-19.
[k] Immunocompromised panel may include CBC with differential, bacterial culture, and Gram stain; AFB culture and stain; fungal immunoassay, culture, and silver stain; CMV, HSV, *Pneumocystis jirovecii* pneumonia (PJP), and respiratory virus PCR.
[l] Treat until symptoms improve to Grade ≤1, then taper over 4–6 weeks.
[m] If clinically indicated and appropriate, monitoring can be done with telemedicine.
[n] In people with pre-existing/underlying lung compromise, greater clinical suspicion and caution should be taken.

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ASSESSMENT/ GRADING	MANAGEMENT[f]
Severe (G3–4)[e] pneumonitis[a]	• Discontinue immunotherapy[g] • Inpatient care • Pulmonary and infectious disease consultation • Minimally invasive evaluation ▸ Infectious workup: ▸ Consider that the patient may be immunocompromised ◊ Nasal swab for potential viral pathogens[j] ◊ Sputum culture (including bacterial, fungal, and AFB), blood culture, and urine antigen test (pneumococcus, legionella) ◊ Consider cardiac evaluation to exclude cardiac causes for clinical presentation • Invasive evaluation ▸ Bronchoscopy with BAL (send for institutional immunocompromised panel[k]) if feasible to rule out infection and malignant lung infiltration and consider transbronchial lung biopsy if feasible and clinically indicated • Consider empiric broad-spectrum antibiotics (including coverage for atypical pathogens) if infection has not yet been fully excluded • IV methylprednisolone 1–2 mg/kg/day. Assess response within 48 hours and plan taper over ≥6 weeks[f] • Consider adding any of the following if no improvement after 48 hours[o]: ▸ IV infliximab[p] 5 mg/kg, a second dose may be repeated 14 days later at the discretion of the treating provider ▸ IVIG[q] ▸ Mycophenolate mofetil 1–1.5 g BID then taper in consultation with pulmonary service[r]

[a] Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging). Symptoms may include dry cough, shortness of breath, fever, chest pain, and increased oxygen requirement. The imaging features of pneumonitis are known to be variable and may include ground-glass opacities, organizing pneumonia, hypersensitivity, reticulonodular changes, or a mixture of all these appearances.
[e] G3-severe symptoms involve all lung lobes or >50% of lung parenchyma; limiting self-care ADLs, oxygen indicated; G4–life-threatening respiratory compromise.
[f] Principles of Immunosuppression (IMMUNO-A).
[g] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[j] Viral pathogen assessment should include COVID-19.
[k] Immunocompromised panel may include CBC with differential, bacterial culture, and Gram stain; AFB culture and stain; fungal immunoassay, culture, and silver stain; CMV, HSV, PJP, and respiratory virus PCR.
[o] Options are listed in alphabetical order. There are no data to support the use of one over another.
[p] An FDA-approved biosimilar is an appropriate substitute for infliximab.
[q] Total dosing should be 2 g/kg, administered in daily divided doses over 2–5 days or as per package insert.
[r] Mycophenolate mofetil is unlikely to improve steroid-unresponsive pneumonitis immediately but may have clinical benefit to avoid steroid-dependence.

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RENAL ADVERSE EVENT(S)

Elevated serum creatinine (sCR)/acute kidney injury (AKI)[a]

ASSESSMENT

- Check BUN, spot urine protein/creatinine ratio, urine microalbumin/creatinine ratio, urine electrolytes (sodium, creatinine),[b] and urinalysis[c]
- Evaluate potential alternative etiologies (recent IV contrast, medications, fluid status, urinary tract infection [UTI])[d]
- Spot urine protein/creatinine ratio[e]
- Microalbumin: creatinine ratio and urinalysis
- Imaging to rule out acute obstructive uropathies

GRADING / **MANAGEMENT[i]**

General: Stage 1, 2, and 3 AKI

- Limit/discontinue nephrotoxic medications and dose adjust to creatinine clearance
- Avoid proton-pump inhibitors [PPIs]; use H2 blockers for GI prophylaxis if initiating corticosteroids
- Consider increased oral/IV hydration and reassess
- Check sCR every 3–7 days

Stage 1 AKI[f]

- Consider holding immunotherapy[j]
- Consider nephrology consult if sustained elevations in creatinine

Stage 2 AKI[g]

- Hold immunotherapy[j]
- Nephrology consultation
- Consider renal biopsy[k] if no improvement within 5–7 days
- Start prednisone 0.5–1 mg/kg/day[l]
- For persistent Stage 2 beyond 1 week, prednisone/IV methylprednisolone 1–2 mg/kg/day[l]

Stage 3 AKI[h]

- Hold immunotherapy[j]
- Consider inpatient care
- Nephrology consultation
- Renal biopsy[k] if no improvement within 5-7 days
- Prednisone/IV methylprednisolone 1–2 mg/kg/day[l]
- Consider adding one of the following if kidney injury remains >Stage 2 after 4–6 weeks of steroids or if creatinine increases during steroid taper (or once off steroids) (in alphabetical order):
  - Azathioprine
  - Infliximab[m,n]
  - Mycophenolate

Footnotes on ICI_RENAL-1A

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FOOTNOTES

[a] Azotemia, creatinine elevation, and inability to maintain acid/base or electrolyte balance.
[b] Rule out pre-renal volume depletion and/or acute tubular necrosis.
[c] Frequency and additional lab tests to be determined in consultation with nephrology to inform treatment.
[d] 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.
[e] For proteinuria >1 g/24-hour with no other etiology for proteinuria present such as diabetes or hypertension and/or gross or microscopic hematuria, check ANA, RF, ANCA, anti-dsDNA, and serum C3, C4, CH50, hepatitis B & C reflexive panels, SPEP, and urine protein electrophoresis (UPEP). For ICI-induced etiologies such as vasculitis and glomerulonephritis, check the following serologies, in addition to obtaining a kidney biopsy: ANA, double-stranded DNA, RF, C3, C4, ANCA, anti-glomerular basement membrane (GBM), hepatitis B and C, HIV, rapid plasma reagin (RPR), SPEP, UPEP, and immunofixation electrophoresis (IFE). Consider 24-hour urine collection.
[f] 1.5 to <2x baseline or increase of ≥0.3 mg/dL over 48 hours.
[g] 2 to <3x baseline.
[h] ≥3.0x baseline; 4.0 mg/dL or need for renal replacement therapy (RRT); dialysis as indicated.
[i] Principles of Immunosuppression (IMMUNO-A).
[j] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[k] Renal biopsy may help distinguish between ICI versus non-ICI–related toxicities; however, initiation of steroids should not be delayed while waiting for biopsy.
[l] Treat until symptoms improve to Grade ≤1, then taper over 4–6 weeks.
[m] An FDA-approved biosimilar is an appropriate substitute for infliximab.
[n] Lin JS, et al. Oncoimmunology 2021;10:1877415.

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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 irAEs.
- Selected irAEs including hypothyroidism and other endocrine irAEs may be treated with hormonal supplementation, without the need for steroid 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.
- Combination therapies with non-ICI agents (eg, VEGF inhibitors) may complicate irAE workup due to overlapping toxicity. If low suspicion of irAE, consider holding non-ICI therapy and monitoring before use of immunosuppression.

Principles of Steroid Use in the Management of irAEs

- Steroids are the mainstay of treatment of most irAEs related to immunotherapy.
- Early intervention with steroids is a key goal in general management of immune-related toxicity.
- Use of steroids to treat irAEs has NOT been shown to reduce anti-tumor efficacy in most cases.[1]
  - In the absence of specific indications such as prior infusion reaction or concurrent chemotherapy, routine premedication with steroids 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, prednisone or IV methylprednisolone 1–2 mg/kg/day) should be given.
  - Higher potency (eg, Class 2 or 3) topical steroids are preferred for short-term use for immune-related dermatitis, compared to longer term use of lower potency steroids.
  - Prednisone is the preferred oral steroid due to ease of dosing and wide availability. IV methylprednisolone is the preferred IV steroid.
- Steroid Taper
  - Longer steroid tapers (>4 weeks, sometimes 6–8 weeks or longer) may be required to prevent recurrent irAE events, particularly pneumonitis, hepatitis, and neuromuscular toxicities.
- Prophylaxis
  - Infection
    - ◊ *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis is recommended for patients expected to receive ≥20 mg daily prednisone equivalent for ≥4 weeks. Consider starting PJP prophylaxis if still steroid-dependent by the end of 2 weeks. Sulfamethoxazole-trimethoprim is preferred. For patients with a sulfa allergy, consider IV pentamidine. Avoid atovaquone due to risk of diarrhea particularly in patients with colitis, and avoid dapsone due to risk of hemolytic anemia. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.
    - ◊ Other fungal infections are rare, and the utility of prophylaxis for these infections is unclear. Patients receiving extended immunosuppression may be at higher risk of an invasive fungal infection.
    - ◊ Prophylaxis against HSV or VZV reactivation can be considered. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.
  - Gastritis
    - ◊ PPI therapy or H2 blockers can be considered for patients at higher risk of gastritis (eg, NSAID use, anticoagulation) for the duration of steroid therapy. Consider prescribing full-dose PPI when the patient is taking high-dose steroids.
  - Osteoporosis
    - ◊ If patients need to be on steroids long-term, 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.

[1] Maslov DV, et al. J Immunother Cancer 2021;9:e002261; Bai X, et al. Clin Cancer Res 2021;27:5993-6000.

Continued

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PRINCIPLES OF IMMUNOSUPPRESSION FOR PATIENTS RECEIVING IMMUNE CHECKPOINT INHIBITOR IMMUNOTHERAPY

Pathogen Reactivation

- There is a risk for hepatitis B virus (HBV) reactivation with anti-TNFα agents, rituximab, or other immunosuppressive agents (eg, steroids). Test for HIV, hepatitis B (surface antigen and core antibodies), and hepatitis C prior to TNF inhibition and monitor HBV/hepatitis C virus (HCV) carriers during and for several months after therapy.
- There is a risk for 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.
- For individuals starting on steroids who were born or who have lived for >3 months in areas endemic for *Strongyloides* such as Central or South America, Southeast Asia, and Africa, would send *Strongyloides* IgG serology and either treat for positive serology, or treat empirically with ivermectin 0.2 mg/kg daily x 2 days and repeat in 2 weeks for total of 4 doses.

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 hematopoietic cell transplant (HCT) 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-programmed cell death protein 1 (PD-1)/programmed death ligand 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[2]

- **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. The risks and benefits of ICI therapy in patients with organ transplantation are very complex. Please refer to transplant team prior to starting immunotherapy in such patients.**
  - **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 HCT

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

[2] Portuguese AJ, et al. J Natl Compr Canc Netw 2022;20:406-416.

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PRINCIPLES OF IMMUNOTHERAPY PATIENT EDUCATION
HEALTH CARE PROVIDER (HCP) INFORMATION

Prior to Starting Immune Checkpoint Inhibitor (ICI) Therapy[a]:

- Assess patient's understanding of disease and recommendations for treatment.
- Educate patients about mechanism of action and rationale for use of ICIs.
- 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 childbearing potential 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 existing educational resources:
  - NCCN Guidelines for Patients
  - Understanding Immunotherapy Side Effects
  - Oncology Nursing Society: Immunotherapy Wallet Cards

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, or mRNA (eg, COVID vaccines) 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.

[a] 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

Toxicity Management[a]:

- **Review patient medications for potential drug interactions (eg, QT prolongation) when administering agents to manage ICI-related toxicity.**
- **Mild to moderate 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.**
  - **Steroids 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 ICIs.**
- **Severe AEs:**
  - **Discontinue immunotherapy.**
  - **Initiate steroid therapy immediately. IV methylprednisolone should be considered until there is evidence of improvement in toxicity.**
  - **Additional immunosuppressant therapy may be required for steroid-unresponsive 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**

[a] 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.
- ICIs are a class of medications that prevent tumors from "hiding" or "evading" the body's natural immune system. ICIs block the proteins referred to above, "releasing the brakes" on the immune system's white blood cells.
- ICI therapy may be given in combination with other ICIs, 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.
- Some immune-related toxicities (eg, inflammatory arthritis, pneumonitis) may become chronic/require long-term management (Braaten TJ, et al. Ann Rheum Dis 2020;79:332-338; Johnson DB, et al. Cancer Immunol Res 2019;7:1755-1759; Naidoo J, et al. J Immunother Cancer 2020;8: e000840).

Monitoring and Treatment Response[a]:

- Therapy with ICIs requires close communications between patient/family and the treating center. Symptoms that patients may think are unrelated (eg, diarrhea or nausea) are often signs of ICI toxicity.
- Educate patients to notify all HCPs (especially PCPs) 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).
- Assess 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.

[a] Principles of Routine Monitoring for Immune Checkpoint Inhibitors (IMMUNO-1).

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PRINCIPLES OF IMMUNOTHERAPY RECHALLENGE

General Principles

- **Discuss the risks/benefits of restarting immunotherapy with the patient.**
- **About 1 in 3 patients may have recurrence of the same irAE after rechallenge.[a] Exercise caution when considering resumption of immunotherapy after significant irAEs. With some exceptions, resumption of immunotherapy following grade 2–3 irAEs can be considered on resolution to ≤ grade 1. Monitor closely for recurrent symptoms.**
  - **If re-challenged and toxicity returns, permanently discontinue class of immunotherapy.**
  - **If an objective response (complete or partial) to ICI therapy was achieved, resumption of immunotherapy may not be necessary. The risk of toxicity on resumption may outweigh benefit.**
- **IrAEs that respond to immunosuppressive therapies may pose a lower risk for rechallenge.**
- **Permanent discontinuation of a given class of immunotherapy may be warranted for severe irAEs or for some moderate irAEs with high risk of morbidity/mortality. 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.**
- **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

Cardio-vascular	• Permanent discontinuation is warranted in the setting of grade 2–4 myocarditis.
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. • Hypophysitis manifested by deficiency of ACTH, TSH, and/or gonad-stimulating hormones, but without symptomatic pituitary swelling: Immunotherapy may continue while replacement endocrine therapy is regulated. • Hypophysitis accompanied by symptoms of pituitary swelling (eg, headache, vision disturbance, and/or neurologic dysfunction): Hold immunotherapy until resolution of symptoms after steroid therapy; consider resumption of immunotherapy after symptoms related to mass effect are resolved. • T1DM with DKA: Consider resuming once DKA has been corrected and glucose level has stabilized. • Primary adrenal insufficiency: After appropriate replacement endocrine therapy is instituted, immunotherapy may continue.
Eye	• Grade 2–4 irAE: Hold immunotherapy per guideline; consider resumption of immunotherapy in consultation with ophthalmology on resolution to ≤ grade 1.
GI	• After grade 2–3 colitis, may consider resumption of immunotherapy after symptoms have resolved to ≤ grade 1. The risk of recurrent colitis is dependent on agent and/or combination resumed (ie, CTLA4 +/- PD-1>PD-1+ LAG3>PD-1). In rare circumstances in which the patient cannot completely taper off steroids, immunotherapy may be resumed while patient is still on ≤10 mg prednisone equivalent daily. Consider concurrent vedolizumab on immunotherapy resumption. • Discontinue if irAE is serious or life-threatening. Do not make up doses missed due to irAE and/or required steroid treatment.

[a] Dolladille C, et al. JAMA Oncol 2020;6:865-871.

Continued

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PRINCIPLES OF IMMUNOTHERAPY RECHALLENGE

Organ-Specific Considerations for Immunotherapy Rechallenge After a Hold

Kidney	• Hold immunotherapy per guidelines; on resolution to ≤Stage 1, consider resuming concomitant with or without steroid if creatinine is stable. • After restarting immunotherapy, monitor creatinine every 2–3 weeks or more frequently as clinically indicated. If creatinine remains stable, consider longer durations between creatinine checks. • Consider permanent discontinuation in the setting of severe (grade 3–4) proteinuria. (Discussion). • For resolved Stage 2 and/or Stage 3 renal irAE, consider permanent discontinuation if possible; may consider re-challenge if clinically indicated, at least after ≥2 months of holding ICI therapy. • If the patient has partial or complete recovery after AKI, consider rechallenge after discussion with nephrology.
Liver	• Transaminitis without synthetic liver dysfunction: Following a grade 2 irAE, may consider resumption of immunotherapy after ALT/AST return to baseline and steroids, if used, have been tapered to ≤10 mg prednisone equivalent daily. • Permanently discontinue immunotherapy in the setting of G4 synthetic liver dysfunction and/or permanent biliary strictures requiring endoscopic retrograde cholangiopancreatography (ERCP).
Lung	• Progressive grade 1 pneumonitis requiring a hold: Consider resuming on radiographic evidence of improvement. • Grade 2: Resume once pneumonitis has resolved to ≤ grade 1 and patient is off steroids. Resume once pneumonitis has resolved to ≤ grade 1 and patient is on a steroid dose of ≤10 mg/day of prednisone. • Permanent discontinuation is warranted in the setting of severe (grade 4) pneumonitis.
Musculo-skeletal	• Inflammatory arthritis, myositis, PMR, GCA (moderate to severe irAE requiring hold): Resume on stabilization, or adequate management of symptoms. Permanent discontinuation may be warranted for severe inflammatory arthritis, PMR, or GCA that significantly impairs ADLs and quality of life. • Severe myositis (with or without myocarditis): Permanent discontinuation is recommended due to high risk of morbidity/mortality
Nervous System	• Myasthenia gravis: Permanently discontinue immunotherapy after grade 3–4 AE. • GBS: Discontinue immunotherapy for severe (grade 3–4) GBS. • Peripheral neuropathy: Following hold for grade 1–2 AE, consider resuming if symptoms resolve to ≤ grade 1 or if patient has well-controlled isolated painful sensory neuropathy. • Aseptic meningitis: Consider resuming following mild to moderate AE if symptoms resolve to grade 0. • Encephalitis: Discontinuation is warranted in the setting of severe encephalitis. • Demyelinating disease: Discontinuation of immunotherapy following any-grade AE.

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Continued

PRINCIPLES OF IMMUNOTHERAPY RECHALLENGE

Organ-Specific Considerations for Immunotherapy Rechallenge After a Hold

Oral Mucosa	• Consider rechallenge after symptoms become grade 1, or mild in the case of oral dysesthesia. • Discuss risks of potential worsening symptoms compared with benefits for patients with moderate to severe Sicca or dysesthesia symptoms.
Pancreas	• Symptomatic grade ≤3 pancreatitis: Consider resumption of immunotherapy if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase. Consider consultation with relevant pancreatic specialist regarding resumption. • Permanent discontinuation is warranted for severe (grade 4) pancreatitis.
Skin	• Maculopapular rash and/or pruritus: Consider resuming after symptoms have resolved to ≤ grade 1 (ie, once skin condition is mild/localized with only topical intervention indicated). • Permanent discontinuation of immunotherapy in the setting of severe or life-threatening bullous disease (grade 3–4), including all cases of SJS and TEN. • Psoriasis and lichen planus: Rechallenge may be considered if symptoms are controlled and extent of BSA is <30%, especially if the patient is on targeted biologic or other inhibitor of the immune response.

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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
• Baseline cardiac assessment, such as echocardiogram. Consult with cardiology if previous cardiac history or concern from assessment. • Perform central venous access, preferably with double or triple lumen catheter, for IV fluid and possible vasopressors use. • 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. • Tumor lysis prophylaxis and monitoring are recommended for patients with large tumor burden and aggressive histologies, as per standard institutional guidelines. • 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 hours for 30 days). • Baseline neurologic evaluation, including ICE scores (for adults) or Cornell Assessment of Pediatric Delirium (CAPD) scores (for children <12 years) prior to CAR T-cell therapy. Consider baseline brain MRI. • Baseline CRP and serum ferritin	• Hospitalization or extremely close outpatient monitoring at centers with CAR T-cell 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. • Hospitalization is warranted for patients at the first sign of CRS or neurotoxicity (including fever, hypotension, or change in mental status). • Monitor CBC, CMP (including magnesium and phosphorus), and coagulation profile daily. • CRP and serum ferritin should be rechecked 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. • Vital signs to allow clinical assessment for CRS should be done at least every 8 hours, or when the patient's status changes, during the peak window of CRS risk (typically the first 1–2 weeks post-infusion). • Neurotoxicity assessment should be done at least twice daily until hospital discharge, and urgently thereafter if there is a change in the patient's status or routinely every 2–4 weeks, extending to 2 months. Consider a physical assessment and/or tests to check handwriting and general function/gait (eg, Timed Get Up and Go [TUG] test). If neurologic concern develops, more frequent assessments are recommended. • Monitor for CRS, neurotoxicity, and other toxicities for the duration recommended by the CAR product package insert (at least 4 weeks and up to 3–6 months post-infusion [depending on the product used] for most patients). Patients should refrain from driving or hazardous activities for at least 8 weeks following infusion.

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

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OVERVIEW OF CAR T-CELL THERAPY-RELATED TOXICITIES

	Axicabtagene Ciloleucel, Brexucabtagene Autoleucel, Ciltacabtagene Autoleucel, Idecabtagene Vicleucel, Lisocabtagene Maraleucel, and Tisagenlecleucel[a]
CRS (CART-5)	• Typical time to onset: 2–3 days; however, CRS may occur as early as hours after infusion and as late as 10–15 days post-infusion; be aware of the typical onset for the specific product used. • Typical duration: 7–8 days; could be longer for specific products. • Manifestation may include fever, hypotension, tachycardia, hypoxia, and chills. CRS may be associated with cardiac, hepatic, and/or renal dysfunction. Consider cardiology follow-up for these symptoms. • Serious events may include hypotension, hypoxia, atrial fibrillation and ventricular tachycardia, cardiac arrest, cardiac failure, renal insufficiency, and capillary leak syndrome.[b]
Neurologic Toxicity/ Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) (CART-6)	• Typical time to onset: 4–10 days • Typical duration: 14–17 days • Transient neurologic symptoms can be heterogeneous and include encephalopathy, delirium, aphasia, lethargy, headache, tremor, myoclonus, dizziness, motor dysfunction, ataxia, sleep disorder (eg, insomnia), anxiety, agitation, and signs of psychosis. • Serious events including seizures, depressed level of consciousness, as well as fatal and serious cases of cerebral edema have occurred.
Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome (IEC-HS) (CART-5)	• Criteria for considering IEC-HS (previously called Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome [HLH/MAS]): ▸ Elevated ferritin (>2 x ULN or baseline [at time of infusion]) and/or rapidly rising (per clinical assessment) ▸ For other criteria to identify IEC-HS and treatment options, refer to: Hines MR, et al. Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome. Transplant Cell Ther 2023;29:438.e1-438.e16.

[a] See Prescribing Information for each agent and institutional protocols.
[b] Alvi RM, et al. J Am Coll Cardiol 2019;74:3099-3108; Ghosh AK, et al. JACC CardioOncol 2020;2:97-109.

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OVERVIEW OF CAR T-CELL THERAPY-RELATED TOXICITIES

	Axicabtagene Ciloleucel, Brexucabtagene Autoleucel, Ciltacabtagene Autoleucel, Idecabtagene Vicleucel, Lisocabtagene Maraleucel, and Tisagenlecleucel[a]
Prolonged Cytopenias	• Patients may exhibit cytopenias for weeks to months following lymphodepleting chemotherapy and CAR T-cell therapy infusion.[c] ▸ First-line management of cytopenias should be standard transfusion and growth factor support as needed. ▸ Optimal management of patients with severe cytopenias refractory to standard management is still unclear; stem cell boosts can be considered if available, although data on this treatment are limited.
Infection and Hypogammaglobulinemia	• Recommend VZV and PJP prophylaxis for at least 3–6 months following CAR-T treatment. • Long-term B-cell aplasia and hypogammaglobulinemia can occur in patients with a complete remission after CAR T-cell therapy infusion. ▸ After anti-CD19 CAR T-cell therapy, consider monthly up to 400–500 mg/kg IVIG replacement for select patients with hypogammaglobulinemia (those with serum IgG levels <400 to 600 mg/dL AND serious or recurrent infections [particularly sinopulmonary]). Continue IVIG until serum IgG levels normalize and infections resolve. The optimal IgG threshold to use may depend on patient characteristics and infection frequency/severity.

[a] See Prescribing Information for each agent and institutional protocols.
[c] Consider G-CSF for as long as necessary; however, GM-CSF is not recommended in the setting of CAR T-cell therapy. An FDA-approved biosimilar is an appropriate substitute for filgrastim.

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TOXICITIES SPECIFIC TO ANTI-BCMA CAR T-CELL THERAPY

	Ciltacabtagene Autoleucel and Idecabtagene Vicleucel[a]
Other neurotoxicity events[f]	• Emerging data suggests that other neurotoxicity events, with symptoms that do not fit the current definition for ICANS, may occur with anti-BCMA CAR T-cell therapy. • Typical time to onset is 11-108 days (later than ICANS) • **Movement and neurocognitive treatment-emergent adverse events (MNTs)** ▸ Manifestation is similar to Parkinson's disease with bradykinesia, asymmetric action and rest tremor, postural instability, hypophonia, personality change, and impaired memory.[d] ▸ Risk factors include high baseline tumor burden, grade ≥2 CRS, prior ICANS, high CAR T cell expansion/persistence.[e] There appears to be male predominance among the reported cases. ▸ Optimal management has not been determined. The characterized cases of MNTs are levodopa unresponsive. ◊ For mild symptoms, consider steroids such as 10 mg dexamethasone daily. ◊ For persistent, severe, or refractory symptoms, and if high circulating CAR T cell levels are detected,[e] consider chemotherapy such as cyclophosphamide to ablate the CAR T cells. ◊ Use of these therapies is currently based on very limited experience and should be balanced against potential safety concerns, such as infection risk. • **Peripheral neuropathy** ▸ Types of neuropathies reported include lower motor neuron facial paralysis, other cranial nerve palsy, peripheral sensory neuropathy, and peripheral motor neuropathy. ▸ For mild symptoms, consider treatment with steroids. ▸ Consider IVIG for acute inflammatory demyelinating polyneuropathy (AIDP)-type picture.

[a] See Prescribing Information for each agent and institutional protocols.
[d] Other signs and symptoms may include: micrographia, flat affect, reduced facial expression, bradyphrenia, hypomimia, impaired balance, bradykinesia, cogwheel rigidity, gait disturbance, rigidity, abnormal posture, decreased stride length, neurocognitive impairment.
[e] Absolute lymphocyte count (ALC), when very elevated, may be a surrogate for high CAR T cell expansion in this setting.
[f] Cohen AD, et al. Blood Cancer J 2022;12:32; Graham CE, et al. Blood 2023;142:1248-1252; Idecabtagene vicleucel package insert; Ciltacabtagene autoleucel package insert.

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CYTOKINE RELEASE SYNDROME (CRS)[g,h]

- 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 patient with neutropenia. Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.[i]
- 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 not required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension or hypoxia.

CRS Grade	Anti-IL-6 Therapy	Steroids[o,p,q]	Additional Supportive Care
Grade 1 Fever (≥38°C)	For prolonged CRS (>3 days)[l] in patients or those with significant symptoms, comorbidities, and/or are >65 years, consider 1 dose of IV tocilizumab 8 mg/kg over 1 hour (not to exceed 800 mg)[m,†,n]	For idecabtagene and lisocabtagene, consider IV dexamethasone 10 mg every 24 hours for early-onset CRS (<72 hours after infusion)[r]	• Sepsis screen and empiric broad-spectrum antibiotics, consider granulocyte colony-stimulating factor (G-CSF) if neutropenic[v] • Maintenance IV fluids for hydration • Symptomatic management of organ toxicities
Grade 2 Fever with hypotension not requiring vasopressors and/or hypoxia[j] requiring low-flow nasal cannula[k] or blow-by	IV tocilizumab 8 mg/kg over 1 hour (not to exceed 800 mg/dose).[n,o] 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: Consider IV dexamethasone 10 mg every 12–24 hours depending on product[a,r,s]	• IV fluid bolus as needed • For persistent refractory hypotension after two fluid boluses and anti-IL-6 therapy: Start vasopressors, consider transfer to ICU, consider echocardiogram, and initiate other methods of hemodynamic monitoring. Telemetry, ECG, troponin, and BNP if persistent tachycardia • Manage per Grade 3 if no improvement within 24 hours after starting anti–IL-6 therapy • Symptomatic management of organ toxicities
Grade 3 Fever with hypotension requiring a vasopressor with or without vasopressin and/or hypoxia requiring high-flow cannula,[k] face mask, nonrebreather mask, or Venturi mask	Anti-IL-6 therapy as per Grade 2[o] if maximum dose not reached within 24-hour period	IV dexamethasone 10 mg every 6–12 hours depending on the product.[a,r] If refractory, manage as grade 4	• Transfer to ICU, obtain echocardiogram, and perform hemodynamic monitoring • Supplemental oxygen • IV fluid bolus and vasopressors as needed • Symptomatic management of organ toxicities
Grade 4 Fever with hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring positive pressure (eg, continuous positive airway pressure [CPAP], bilevel positive airway pressure [BiPAP], intubation, mechanical ventilation)	Anti-IL-6 therapy as per Grade 2[o] if maximum dose not reached within 24-hour period	IV dexamethasone 10 mg every 6 hours.[r] If refractory, consider 3 doses of IV methylprednisolone 1–2 g/day depending on the product.[a] If refractory, consider dosing every 12 hours.[t] Other lines of therapy may be considered[u]	• ICU care and hemodynamic monitoring • Mechanical ventilation as needed • IV fluid bolus and vasopressors as needed • Symptomatic management of organ toxicities

Footnotes on CART-5A

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FOOTNOTES

[a] See Prescribing Information for each agent.
[g] If IEC-HS is suspected, refer to treatment options in Hines MR, Knight TE, McNerney KO, et al. Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome. Transplant Cell Ther 2023;29:438.e1-438.e16.
[h] 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;25:625-638. 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 Derivatives License (CC BY NC ND).
[i] Organ toxicities should receive a thorough workup and appropriate management.
[j] 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.
[k] 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.
[l] For axicabtagene ciloleucel or brexucabtagene autoleucel, can consider tocilizumab if CRS symptoms persist for >24 hours.
[m] For lisocabtagene maraleucel, consider tocilizumab for grade 1 CRS that develops <72 hours after infusion and consider adding dexamethasone 10 mg x 1. For CRS developing ≥72 hours after infusion, treat symptomatically.
[n] An FDA-approved biosimilar is an appropriate substitute for tocilizumab.
[o] After each dose, assess need for subsequent dosing.
[p] Antifungal prophylaxis and close monitoring for breakthrough infections per institutional guidelines should be strongly considered in patients receiving steroids for the treatment of CRS and/or neurotoxicity.
[q] Per the prescribing information for axicabtagene ciloleucel, consider the use of prophylactic steroids in patients after weighing the potential benefits and risks. Steroid prophylaxis for axicabtagene ciloleucel is dexamethasone 10 mg orally once daily for 3 days with the first dose starting pre-CAR T-cell infusion.
[r] Alternative steroids at an equivalent dose may be considered.
[s] For axicabtagene ciloleucel, consider IV dexamethasone 10 mg every 24 hours after initial tocilizumab dosing, regardless of clinical response to tocilizumab. For lisocabtagene maraleucel, consider IV dexamethasone 10 mg every 12–24 hours if early-onset CRS. For idecabtagene vicleucel, consider IV dexamethasone 10 mg every 12–24 hours.
[t] For example, IV methylprednisolone 1000 mg/day for 3 days, followed by rapid taper at 250 mg every 12 hours for 2 days, 125 mg every 12 hours for 2 days, and 60 mg every 12 hours for 2 days.
[u] Anakinra may be considered as the first choice for severe CRS refractory to anti–IL-6 therapy and high dose corticosteroids. Other agents such as siltuximab, ruxolitinib, cyclophosphamide, IVIG, ATG, intrathecal chemotherapy, or extracorporeal cytokine adsorption with continuous renal replacement therapy (CRRT) may also be considered, although experience with these agents is limited. Use of these therapies should be balanced against potential safety concerns, such as infection risk.
[v] GM-CSF is not recommended in the setting of CAR T-cell therapy. An FDA-approved biosimilar is an appropriate substitute for filgrastim.

[†] Under conditions of limited tocilizumab availability, consider one of the following conservation strategies:
- Limit tocilizumab use to a maximum of 2 doses during a CRS episode.
- Consider using steroids more aggressively during a CRS episode.
- If necessary, consider replacing second dose of tocilizumab with siltuximab or anakinra, although there is very limited evidence to support this approach.

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CAR T-CELL–RELATED NEUROTOXICITY GRADING

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

- **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**

ASTCT Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) Consensus Grading for Adults[h]

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.

Neurotoxicity Domain[w]	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[x]	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness[y]	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[z]	Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad

[h] 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;25:625-638. 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 Derivatives License (CC BY NC ND).

[w] 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.

[x] 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.

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

[z] 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.

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.

Treatment (CART-7)

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 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[cc]	Additional Therapy if Concurrent CRS
Grade 1[aa]	• Supportive care	IV tocilizumab 8 mg/kg over 1 hour (not to exceed 800 mg/dose)[n,ff,†]
Grade 2	• Supportive care • 1 dose of IV dexamethasone 10 mg and reassess. Can repeat every 6–12 hours, if no improvement.	Anti-IL-6 therapy as per Grade 1[ff] Consider transferring patient to ICU if neurotoxicity associated with grade ≥2 CRS
Grade 3[bb]	• ICU care is recommended • IV dexamethasone 10 mg every 6 hours or IV methylprednisolone, 1 mg/kg every 12 hours[p,dd] • 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[ff]
Grade 4[bb]	• ICU care, consider mechanical ventilation for airway protection • High-dose steroids.[p,ee] If unresponsive to steroids, consider adding anakinra 100 mg q 6 h. • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 neurotoxicity • Treat convulsive status epilepticus per institutional guidelines	Anti-IL-6 therapy as per Grade 1[ff]

† Under conditions of limited tocilizumab availability, consider one of the following conservation strategies:
- Limit tocilizumab use to a maximum of 2 doses during a CRS episode.
- Consider using steroids more aggressively during a CRS episode.
- If necessary, consider replacing second dose of tocilizumab with siltuximab or anakinra, although there is very limited evidence to support this approach.

n An FDA-approved biosimilar is an appropriate substitute for tocilizumab.

p Antifungal prophylaxis and close monitoring for breakthrough infections per institutional guidelines should be strongly considered in patients receiving steroids for the treatment of CRS and/or neurotoxicity.

aa For lisocabtagene maraleucel or idecabtagene vicleucel, if ICANS develops <72 hours after infusion, consider IV dexamethasone 10 mg every 12–24 hours x 2 doses and reassess.

bb Patients should undergo assessment for papilledema or other signs of elevated intracranial pressure. If intracranial pressure is excluded, a diagnostic lumbar puncture may be considered for patients with grade 3–4 neurotoxicity.

cc If dexamethasone is used for prophylaxis of CRS, there may be an increased risk of grade 4 and prolonged neurologic toxicities.

dd For axicabtagene ciloleucel or brexucabtagene autoleucel, IV methylprednisolone 1 g daily for 3–5 days may be preferable.

ee For example, IV methylprednisolone 1000 mg/day (may consider twice a day) for 3 days, followed by rapid taper at 250 mg every 12 h for 2 days, 125 mg every 12 hours for 2 days, and 60 mg every 12 hours for 2 days.

ff 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.

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.

OVERVIEW OF LYMPHOCYTE ENGAGER-RELATED TOXICITIES

General Principles

- **Clinicians should refer to the individual FDA approved package insert and appropriate clinical trial protocols for guidance on toxicity management. Institutions administering these therapies should have clear, agent-specific protocols in place to facilitate timely management of severe reactions such as CRS, ICANS and other toxicities.**
- **CD3-based lymphocyte engager therapies carry a universal risk of CRS. CRS risk requires frequent monitoring and early intervention to prevent progression to severe or refractory CRS. (See CART-5 for CRS grading; refer to the FDA approved package insert for guidance on CRS management).**
- **Due to risk of CRS, lymphocyte engager therapies generally require inpatient initiation for monitoring, with transition to ambulatory settings dictated by patient tolerability.**
- **Consider providing patients with one dose of dexamethasone 8 mg to take if needed for severe CRS (eg, shaking chills, difficulty breathing, feeling severely ill) at home prior to travel to Emergency Department if instructed to do so.**
- **ICANS is a central nervous system toxicity associated with lymphocyte engager therapy. ICANS is characterized by neurologic deficits, often concomitantly with CRS. These deficits can be serious and progressive, and may include aphasia, altered mental status, weakness, reduced cognition, motor dysfunction, seizures, and/or cerebral edema.[1] (See CART-6 and CART-7 for Assessment/Grading; refer to FDA approved package insert for guidance on ICANS management).**
- **Other common unique toxicities vary based on agent:**
  - **Examples: blinatumomab (neurologic), tebentafusp-tebn (dermatologic; liver enzyme elevation), teclistamab-cqyv (infection and cytopenias; neurologic), and mosunetuzumab-axgb (neurologic; cytopenias)**

[1] 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;25:625-638.

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.

ABBREVIATIONS

AChR	acetylcholine receptor
ACTH	adrenocorticotropic hormone
ADEM	acute demyelinating encephalomyelitis
ADL	activities of daily living
AE	adverse event
AFB	acid-fast bacilli
AIDP	acute inflammatory demyelinating polyneuropathy
AKI	acute kidney injury
ALC	absolute lymphocyte count
ALT	alanine transaminase
ANA	antinuclear antibody
ANCA	antineutrophil cytoplasmic antibody
ASMA	anti-smooth cell antigen
AST	aspartate transaminase
ASTCT	American Society for Transplantation and Cellular Therapy
ATG	antithymocyte globulin
BAL	bronchoalveolar lavage
BiPAP	bilevel positive airway pressure
BNP	b-type natriuretic peptide
BRAT	bananas, rice, apple sauce, toast
BSA	body surface area
BUN	blood urea nitrogen
CAPD	Cornell Assessment of Pediatric Delirium
CAR	chimeric antigen receptor
CBC	complete blood count
csDMARD	conventional synthetic disease modifying anti-rheumatic drug
CCP	cyclic citrullinated peptide
CGM	continuous glucose monitoring
CK	creatine kinase
CMP	comprehensive metabolic panel
CMV	cytomegalovirus
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
CPK	creatinine phosphokinase
CRRT	continuous renal replacement therapy
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
CTCAE	common terminology criteria for adverse events
DKA	diabetic ketoacidosis
DM	diabetes mellitus
DRESS	drug rash with eosinophilia and systemic symptoms
EBV	Epstein-Barr virus
ECG	electrocardiogram
EEG	electroencephalogram
EGD	esophagogastroduodenoscopy
EMG	electromyography
ENT	ear, nose, and throat
ERCP	endoscopic retrograde cholangiopancreatography
ESR	erythrocyte sedimentation rate
FSH	follicle-stimulating hormone
GBM	glomerular basement membrane
GBS	Guillain-Barré syndrome

Continued

ABBREVIATIONS

GCA	giant cell arteritis
G-CSF	granulocyte colony-stimulating factor
GI	gastrointestinal
GM-CSF	granulocyte-macrophage colony stimulating factor
GVHD	graft-versus-host disease
H&P	history and physical
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCP	health care provider
HCT	hematopoietic cell transplant
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLH	hemophagocytic lymphohistiocytosis
HSV	herpes simplex virus
iADL	instrumental activities of daily living
ICANS	immune effector cell-associated neurotoxicity syndrome
ICE	immune effector cell-associated encephalopathy
ICI	immune checkpoint inhibitor
ICI-T1DM	immune checkpoint inhibitor-associated type 1 diabetes mellitus
ICU	intensive care unit
ID	infectious disease
IEC-HS	immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome
IFE	immunofixation electrophoresis
IgE	immunoglobulin E
IgG	immunoglobulin G
IL-6	interleukin-6
INR	International normalized ratio
IO	immuno-oncology
irAE	immune-related adverse event
IVIG	intravenous immunoglobulin
LFT	liver function test
LH	luteinizing hormone
LV	left ventricular
LVEF	left ventricular ejection fraction
MAS	macrophage activation syndrome
MGFA	Myasthenia Gravis Foundation of America
MNT	movement and neurocognitive treatment-emergent adverse event
MRCP	magnetic resonance cholangiopancreatography
NAAT	nucleic acid amplification test
NCS	nerve conduction study
NIF	negative inspiratory force
NSAID	nonsteroidal anti-inflammatory drug
NTproBNP	N-terminal prohormone B-type natriuretic peptide
PCP	primary care physician
PCR	polymerase chain reaction
PD-1	programmed cell death protein 1
PD-L1	programmed death ligand 1
PE	pulmonary embolism
PFT	pulmonary function test
PJP	*Pneumocystis jirovecii* pneumonia
PMR	polymyalgia rheumatica

Continued

ABBREVIATIONS

PPI	proton pump inhibitor
PT	Prothrombin time
PUD	peptic ulcer disease
RF	rheumatoid factor
RPR	rapid plasma reagin
RRT	renal replacement therapy
SCR	serum creatinine
SJS	Stevens-Johnson syndrome
SPEP	serum protein electrophoresis
T4	free thyroxine
TB	tuberculosis
TEN	toxic epidermal necrolysis
TFT	thyroid function test
Tg	thyroglobulin
TNF	tumor necrosis factor
TPN	total parenteral nutrition
TPO	thyroid peroxidase
TRAb	TSH receptor antibody
TSH	thyroid-stimulating hormone
TSI	thyroid-stimulating immunoglobulin
TTE	transthoracic echocardiogram
ULN	upper limit of normal
UPEP	urine protein electrophoresis
UTI	urinary tract infection
UVB	ultraviolet B
VC	vital capacity
VEGF	vascular endothelial growth factor
VZV	varicella zoster virus
WBC	white blood cell

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 corresponds to the NCCN Guidelines for Management of Immunotherapy-Related Toxicities. The CAR-T cell therapy section was added on February 28, 2022. All other sections were last updated on April 8, 2019.

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 versus 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 jirovecii* 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]

<u>NCCN Recommendations</u>

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

Chimeric antigen receptor (CAR) T-cells represent a newer class of immunotherapy agents that is increasingly being incorporated into the treatment regimens of certain refractory or relapsed hematological malignancies, specifically subtypes of B-cell non-Hodgkin lymphoma (NHL), adult and pediatric B-cell acute lymphoblastic leukemia (ALL), and multiple myeloma (MM). CAR T-cells are genetically reprogrammed T-cells that express CARs, synthetic receptors that can be designed to target tumor surface antigens.[257,258] This treatment is a type of adoptive cell therapy and can be referred to as a "living drug."[259] The intent of CAR T-cell therapy is to induce a potent anti-tumor immune response by merging the specificity of an antibody with the cytotoxic and memory functionality of T-cells.[258,260,261] Currently approved CAR T-cell anti-cancer therapies are generated from autologous T lymphocytes that are genetically modified to recognize and kill tumor cells that express specific antigens.[262-266] While CAR T-cell therapy has uniquely powerful activity in several B-cell malignancies, it is also accompanied by specific toxicities requiring specialized expertise in management. This text provides an overview of CAR T-cell therapies and NCCN recommendations for the management of CAR T-cell-related toxicities in patients with cancer based on available evidence and clinical experience. For a discussion of the efficacy data for CAR T-cell therapies, see the NCCN Guidelines for Treatment of Cancer by Site at www.NCCN.org.

Design and Structure of CARs

CARs are engineered proteins that include an antigen recognition domain, a hinge region, a transmembrane domain, and at least 1 intracellular domain (Figure 1).[259,267,268] The antigen recognition domain is an extracellular targeting domain derived from a single chain fragment variable (scFv) that mimics an antibody's antigen binding region and recognizes specific antigens expressed on the surface of tumor cells in a human leukocyte antigen (HLA) independent manner. For currently approved CAR T-cells, the scFv recognizes either cluster of differentiation 19 (CD19), for B-ALL and B-NHL, or B-cell maturation antigen (BCMA), for MM.[262-266] Some agents under investigation have antigen recognition domains with a different structure or target novel antigens. For example, the antigen recognition domain of ciltacabtagene autoleucel is comprised of 2 llama-derived single variable domain on a heavy chain (VHH) domains that can bind 2 distinct BCMA epitopes.[269]

CAR T-cell therapies typically have an immunoglobulin (Ig)-like hinge domain that separates the antigen recognition domain from the transmembrane domain.[270] Approved agents have an IgG4, CD28, or CD8α hinge domain.[262-266] Optimization of this domain may increase access to the antigen and improve the efficiency of CAR expression and activity.[270]

It is critical for CAR constructs to have a transmembrane domain, which enables the CARs to be embedded within the T-cell membrane, and may contribute to CAR T-cell signaling.[270] Most available CAR T-cell therapies use a CD8α or CD28 transmembrane domain.[262-266]

Early studies also found that CAR constructs require a domain to activate T-cells, also known as a T-cell activation domain.[259] All approved agents utilize a CD3ζ signaling domain for this function.[262-266]

While the T-cell activation domain was the only intracellular domain included in "first-generation" CAR T-cell constructs, currently available "second-generation" CAR constructs now also include either a CD28 or 4-1BB intracellular co-stimulatory construct.[259,262-266,271] The binding of a co-stimulatory receptor such as CD28 or 4-1BB to its cognate ligand on an antigen-presenting cell (APC) provides an additional signal for normal T-cell activation; therefore, inclusion of a CD28 or 4-1BB co-stimulatory

domain within CAR constructs enhances the activation, proliferation, and anti-tumor activity of CAR T-cells (Figure 1).[271,272] Different co-stimulatory domains appear to be associated with changes in expansion kinetics, persistence, and possibly toxicity.[271] Unfortunately, efforts to evaluate the superiority of each type of co-stimulatory domain based on efficacy and safety data have been inconclusive due to various factors, such as differences in other CAR domains, clinical trial design, and toxicity grading systems.[271] Newer-generation CAR constructs with more or different co-stimulatory domains, as well as with a variety of antigen targets, including solid tumor antigens, are currently under active development.[273]

Targets of Currently Approved CAR T-Cells

CD19

CD19 is a transmembrane glycoprotein that is a member of the immunoglobulin (Ig) superfamily and is an important regulator of B-cell signaling and B-cell activation.[274-277] Due to its expression at all stages of B-cell differentiation, except for hematopoietic stem cells, CD19 is considered a reliable B-cell biomarker.[277-279] Importantly, CD19 is retained on cells that have undergone neoplastic transformation.[277,279] Increased expression of CD19 has been found on most B-cell tumors, including B-cell ALL, chronic lymphocytic leukemia (CLL), and B-cell lymphomas.[278-284] Currently approved CD19 CAR T-cell therapies include tisagenlecleucel, axicabtagene ciloleucel, brexucabtagene autoleucel, and lisocabtagene maraleucel.[262,263,265,266]

BCMA

BCMA is a transmembrane protein that is a member of the tumor necrosis factor receptor (TNFR) superfamily.[285-287] Expressed on the surface of mature B cells, but not naïve B cells or other hematopoietic cells, BCMA is thought to promote the survival of plasma cells in the bone marrow.[285,286,288,289] BCMA was identified as a promising biomarker and drug target for MM based on several findings. Serum BCMA levels were observed to be higher in patients with MM compared to those without MM.[290,291] Multiple studies found that BCMA is expressed in malignant cells from patients with MM.[291-295] Furthermore, overexpression of BCMA promoted cell proliferation in both in vitro and in vivo models.[296] Currently the only BCMA-targeting CAR T-cell therapy approved in the US is idecabtagene vicleucel, which was approved in 2021 for the treatment of MM.[264] Ciltacabtagene autoleucel is another BCMA-targeted CAR T-cell therapy that is being considered by the FDA approval for the treatment of relapsed or refractory MM.[297]

Overall CAR T-Cell Treatment Schema

CAR T-cell therapy is a multistep process that can take several weeks to complete.[298] The first step is leukapheresis, the procedure of collecting white blood cells (including T cells) from a patient's blood.[260,299,300] The cells are subsequently sent to a laboratory, where T cells are isolated, activated, and transduced with a CAR transgene (typically delivered via a lentiviral or retroviral vector). Transduced T cells are then expanded, harvested, and prepped for infusion.[260,299-301] Finally, patients are infused with the CAR T-cells. Prior to infusion, patients undergo lymphodepletion chemotherapy (LDC). The goal of LDC is to prevent immunologic rejection of the infused CAR T-cells in order to maximize their expansion and persistence. LDC typically consists of fludarabine and cyclophosphamide.[262-266,302,303] Bendamustine is an alternative option prior to tisagenlecleucel infusion in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who had a prior Grade 4 hemorrhagic cystitis with cyclophosphamide or developed a resistance to a previous cyclophosphamide containing regimen.[266] Depending on the product, patients may be treated on an inpatient or outpatient basis. However, outpatient therapy requires a robust infrastructure for rapid evaluation and intervention for toxicity.

CAR T-Cell Therapy-related Toxicities and Management Strategies

Despite the promising benefits of CAR T-cell therapies in the treatment of certain cancers, clinicians need to be aware of the serious and potentially fatal toxicities that may occur with the use of this newer class of agents. Overall, the most common and unique toxicities associated with CAR T-cell therapies are cytokine release syndrome (CRS) and neurotoxicity, and are entirely distinct from the immune-related adverse events (irAEs) that occur with the use of immune-checkpoint inhibitors (ICIs). In addition, some toxicities (eg, hypogammaglobulinemia) are a direct result of on-target/off-tumor activity of the CAR T-cells, while others (eg, infections) may occur as an indirect consequence of the immunosuppressed state of the patient. Fortunately, CAR T-cell therapy-related toxicities are almost always reversible and can be managed by the judicious use of immunosuppressive medications.

Principles of Patient Monitoring

The NCCN panel has provided recommendations on monitoring patients who receive CAR T-cell therapies based on available evidence and clinical experience, as detailed below and on CART-1. For effective toxicity management, clinicians need to closely monitor patients before, during, and after CAR T-cell infusions to ensure the early recognition of and intervention for specific adverse reactions related to treatment. Patients with underlying organ dysfunction may experience additional complications when treated with CAR T-cell therapies; proactive management and multidisciplinary involvement is especially crucial for these patients.

Before and During CAR T-Cell Infusion

Due to the potential cardiac manifestations of CAR T-cell-related toxicities, especially for those with underlying risk,[304-307] a baseline cardiac assessment (such as an echocardiogram) is recommended. Consultation with cardiology may be warranted for patients with cardiovascular comorbidities at baseline. Central venous access, preferably with double or triple lumen catheter, for intravenous (IV) fluid and possible vasopressor use is recommended. Cardiac monitoring should be performed at the onset of clinically significant arrhythmia and additionally as clinically indicated. For patients with large tumor burden and aggressive histologies, standard tumor lysis prophylaxis and monitoring are recommended. Seizure prophylaxis (eg, levetiracetam 500-750 mg orally every 12 hours for 30 days) are often used on the day of infusion, especially for CAR T-cell therapies that are known to cause more severe CAR T-cell-related neurotoxicity (eg, axicabtagene and brexucabtagene). Because of the potential for severe neurotoxicity, all patients should receive baseline neurological evaluation, including ICE scores (for adults) or CAPD scores (for children less than 12 years) prior to CAR T-cell therapy. Some centers require baseline brain magnetic resonance imaging (MRI). Assessment of C-reactive protein (CRP) and serum ferritin levels is recommended at baseline.

Post-CAR T-Cell Infusion

Hospitalization or extremely close outpatient monitoring at centers with CAR T-cell experience is recommended. Close monitoring in the hospital is preferred with current products for adults; however, extremely close outpatient monitoring may be possible at centers with outpatient transplant experience. Hospitalization is warranted for patients at the first sign of CRS or neurotoxicity, including fever, hypotension, or change in mental status. Complete blood count (CBC), complete metabolic panel (CMP), (including magnesium and phosphorus) and coagulation profiles should be monitored daily. CRP and serum ferritin should be rechecked at least 3 times per week for 2 weeks post-infusion. Daily levels can be considered if CRS occurs. Vital signs to allow clinical assessment for CRS should be done at least every 8 hours, or when the patient's status changes, during the peak window of CRS risk, which is typically the first

1-2 weeks post-infusion. The time to onset of fever, and therefore CRS, may be earlier in patients treated with CD28 costimulatory domain-containing products (axicabtagene ciloleucel and brexucabtagene autoleucel) compared with 4-1BB costimulatory domain-containing products (tisagenlecleucel, lisocabtagene maraleucel, and idecabtagene vicleucel). Note that CRS may normalize prior to the onset of neurotoxicity. Neurotoxicity assessment (as described below) should be done at least twice daily or when the patient's status changes. This is typically during the first 1-2 weeks post-infusion, but has been seen with later onset up to a month, and very rarely later. If neurologic concern develops, more frequent assessments are recommended. Patients should be monitored for CRS, neurotoxicity, and other toxicities for the duration recommended by the CAR product package insert (at least 4 weeks post-infusion for most patients). Patients should refrain from driving or hazardous activities for at least 8 weeks following infusion.

Management Strategies for Specific CAR T-Cell Therapy-Related Toxicities

An overview of CAR T-cell therapy-related toxicities is shown on CART-2. The presentation and the management of specific toxicities related to CAR T-cell therapies are discussed in the following sections. **It is critical to recognize that the exact timing, frequency, severity, and optimal management of CAR T-cell-related toxicities vary between products, and are likely to vary further as newer products gain approval. The NCCN Guidelines attempt to provide guidance that is generally applicable, but clinicians must imperatively consult their institutional guidelines and the prescribing information for individual agents for specific management strategies.**

Cytokine Release Syndrome (CRS)

CRS has been reported with all FDA approved CAR T-cell therapies and is one of the most common adverse events that occur with both CD19- and BCMA-directed CAR T-cells. Due to the different grading scales used to assess CRS severity in clinical trials, differences in CAR T-cell design and generation, and clinical trial design (including study population, dose regimen, and treatment protocols), a wide range of CRS rates have been reported with different CAR T- cell therapies.[308-315] Therefore, toxicity rates from trials of different agents may not always be directly comparable.

Presentation and onset

CRS is defined by the American Society for Transplantation and Cellular Therapy (ASTCT) as a supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells (eg, lymphocytes, myeloid cells).[316] Specific CRS manifestations may include fever, hypotension, tachycardia, hypoxia, and chills, and may be associated with cardiac, hepatic, and/or renal dysfunction. Serious events that may occur with CRS include hypotension, hypoxia, atrial fibrillation and ventricular tachycardia, cardiac arrest, cardiac failure, renal insufficiency, and capillary leak syndrome. The cardiovascular complications that attend CRS can be severe and even fatal for patients with underlying risk who receive CAR T-cell therapy,[304,305] again highlighting the importance of careful patient selection and close monitoring. The typical time to onset for CRS is 2-3 days, with a duration of 7-8 days, although CRS may occur within hours following CAR T-cell infusion and as late as 10-15 days post-infusion.[308,310-315]

Pathophysiology

The overactivation of immune effector cells lead to the release of inflammatory cytokines, which ultimately results in endothelial injury and

capillary leak that can present clinically as hemodynamic instability and organ dysfunction.[317,318] Multiple cytokines have been implicated in CRS, including IL-6, IL-1, IFN-γ, and TNF-α.[317-323] IL-6 is considered a central mediator of CRS and is thought to provide an activating signal to CAR T-cells.[317] In normal conditions, IL-6 binds to membrane-bound IL-6 receptor (IL-6R) on certain immune effector cells and has anti-inflammatory properties; this is referred to as the classic signaling pathway. However, when IL-6 levels are increased (such as during CRS), IL-6 may bind to the soluble form of IL-6R (sIL-6R) and induce a pro-inflammatory response via activation of a trans signaling pathway.

Risk factors

Several risk factors for severe CRS have been identified, although these vary across studies and likely across indications.[317,318,324-327] These generally (but not always) include increased CAR T-cell expansion and higher tumor burden (including high disease burden in bone marrow).[317,318,326,327]

Grading

The NCCN Guidelines follow the ASTCT Consensus Grading scale for CRS, which used a consensus approach to harmonize the various CRS definitions and grading systems that were previously used in pivotal clinical trials.[316] The grades are defined by presence of fever (≥38°C), the severity of hemodynamic compromise, and that of hypoxia. Fever defines the onset of CRS, with a temperature of ≥38°C not attributable to any other cause being the only symptom required for the classification as grade 1 CRS. Other types of organ dysfunction were not included in the ASTCT grading criteria. Laboratory parameters (eg, CRP or specific cytokines) were also not included in the definition or the grading scale for CRS, as it was deemed that there was insufficient evidence to support their use in this context.[316] However, these parameters may become more important in the future with additional studies. Please refer to CART-3 of the algorithm for the adapted definitions of each CRS grade.

Overall Management Strategy for CRS

Management of CRS in patients who received CAR T-cell therapy consists of both direct targeting and non-specific immunosuppressive strategies to counter the overactive immune cells and increased cytokine levels. Generally, patients are administered a combination of tocilizumab and corticosteroids, in addition to receiving supportive care.

Anti-IL-6 Therapy

Tocilizumab is a humanized, IgG1κ anti-IL6R antibody that was approved by the FDA in 2017 for the treatment of severe or life-threatening CAR T-cell-induced CRS in adults and pediatric patients aged 2 years and older.[328,329] Tocilizumab binds to both soluble and membrane-bound interleukin-6 receptor (IL-6R), and is hypothesized to block the downstream signal transduction pathways implicated in CRS.[330] Tocilizumab is currently the only anti-IL-6 therapy approved by the FDA for the treatment of CRS.

This approval was based on a retrospective study of patients with hematological malignancies who developed severe or life-threatening CRS and received tocilizumab after treatment with tisagenlecleucel (n=45) or axicabtagene ciloleucel (n=15) in prospective trials.[328,329] CRS was resolved within 14 days of the first tocilizumab dose in 69% and 53% of patients in the tisagenlecleucel and axicabtagene ciloleucel cohorts, respectively. No adverse reactions were reported in this study, although infections, cytopenias, elevated liver enzymes, and lipid dysregulation have been reported with tocilizumab use in clinical trials for other conditions.[328,329]

While approved for severe or life-threatening cases, many centers and the prescribing information for individual agents advise using tocilizumab

at lower grades of CRS.[262-265,331] For example, the prescribing information for axicabtagene ciloleucel states that tocilizumab can be considered for Grade 1 CRS if CRS symptoms persist for more than 24 hours.[262] This is supported by data from an exploratory safety management cohort of the ZUMA-1 trial, which demonstrated that patients who received earlier intervention with tocilizumab and/or corticosteroids for CRS (as early as Grade 1) had numerically lower rates of ≥grade 3 CRS (2%) compared with patients who received intervention at later CRS grades (12%).[332]

A proposed alternative to tocilizumab is siltuximab, an anti-IL6 antibody that is approved for the treatment of Castleman's disease.[333] By targeting the same pathway as tocilizumab, siltuximab would theoretically also be a viable treatment option for CRS. An additional potential advantage of siltuximab over tocilizumab is that the latter targets the receptor for IL-6 without sufficient central nervous system (CNS) penetration. This causes a transient rise in serum IL-6 levels, which some have postulated may worsen neurotoxicity by increasing cerebrospinal fluid IL-6 levels.[321,334] This potential increase in the neurotoxicity is an important concern in general with the use of tocilizumab for CRS, and may support the more frequent use of corticosteroids in conjunction with tocilizumab in more recent management guidelines. For persistent refractory CRS after 1-2 doses of tocilizumab, the guideline recommends considering the addition of corticosteroids. Despite the theoretical advantage of the IL-6-targeting siltuximab, there is limited data in the formal clinical trial setting supporting the use of this agent for CRS.[334,335] Anakinra, an IL-1Ra antagonist currently approved for the treatment of several inflammatory conditions,[336] is considered another potential alternative to tocilizumab for the treatment of CRS following CAR T-cell therapy. The rationale for targeting IL-1 is primarily based on evidence from two preclinical studies, which demonstrated that IL-1 blockade protected against CRS in mouse models without impacting the anti-tumor activity of the CAR T-cells.[321,322] While there are some reports in patients that suggest anakinra may be effective for managing CAR T-cell therapy-associated CRS,[337,338] there is also limited data supporting use of anakinra in this setting. Data from ongoing clinical trials will shed light on whether siltuximab and anakinra are viable alternatives to tocilizumab for the treatment of CRS.

Corticosteroids

Corticosteroids play an important role in CRS management in addition to anti-IL-6 therapy. Although the use of corticosteroids may alleviate the symptoms of CRS, there is theoretical concern that the use of higher doses of steroids could suppress CAR T-cell expansion and persistence, and therefore reduce the antitumor benefit of CAR T-cells.[339] However, this concern has not been supported in most studies, and corticosteroids are a cornerstone of CRS management. Furthermore, in the context of axicabtagene, the use of corticosteroids, either with milder CRS (or even prophylactically) appear to be associated with preserved efficacy, lower risk of severe CRS, and lower cumulative use of steroids.[332,340,341] The most commonly used corticosteroids are dexamethasone and methylprednisolone. For patients with neurological symptoms, dexamethasone may be preferred due to better penetration of the blood-brain-barrier.[342] If steroids are used for the management of CRS, a rapid taper should be used once symptoms begin to improve.

Options for steroid-refractory CRS

If CRS does not improve after tocilizumab and steroids, workup for infections need to be considered and managed as appropriate. In addition to siltuximab and anakinra, other agents can be considered for patients who are refractory to both tocilizumab and corticosteroids, including the Janus Associated Kinase (JAK) 1/2 inhibitor ruxolitinib, cyclophosphamide, extracorporeal cytokine adsorption with continuous renal replacement therapy (CRRT), intravenous IgG (IVIG), and anti-thymocyte globulin (ATG); however, data supporting the use of

these agents are mostly anecdotal or from small case series.[262,343-348] This will likely change in the future as results from ongoing clinical trials mature.

NCCN Recommendations for CRS

Urgent intervention is required to prevent the progression of CRS; however, other potential causes of inflammatory response, including infections and malignancy progression, should be ruled out. Empiric treatment for infections is warranted in patients who are febrile and neutropenic. Organ toxicities associated with CRS may be graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, but clinicians should be aware that these do not influence CRS grading under the ASTCT system. Organ toxicities should receive a thorough workup and appropriate management. Fever is defined as a temperature that is above 38°C that is not attributable to any other cause. For patients with CRS who receive antipyretics or anticytokine therapy, such as tocilizumab or steroids, fever is not required to grade subsequent CRS severity. For these cases, hypotension or hypoxia will determine CRS grading. See below (as well as CART-3 and CART-3A) for detailed treatment recommendations for CRS by grade.

In general, after each dose of anti-IL-6 therapy or corticosteroids, the need for subsequent dosing should be assessed. As per the prescribing information for axicabtagene ciloleucel, consider the use of prophylactic corticosteroids in patients after weighing the potential benefits and risks. Steroid prophylaxis for axicabtagene ciloleucel is dexamethasone 10 mg orally once daily for three days, with the first dose starting pre-CAR T-cell infusion; however, use of dexamethasone in this setting may increase the risk of Grade 4 and prolonged neurologic toxicities. Additionally, antifungal prophylaxis should be strongly considered in patients receiving steroids for the treatment of CRS and/or neurotoxicity.

Grade 1 (fever ≥38°C): For prolonged CRS (longer than 3 days) in patients or those with significant symptoms, comorbidities, and/or are elderly, 1 dose of tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg) can be considered. For patients treated with axicabtagene ciloleucel or brexucabtagene autoleucel, tocilizumab can be considered if CRS symptoms persist for >24 hours. For patients treated with lisocabtagene maraleucel, consider tocilizumab for grade 1 CRS that develops <72 hours after infusion, and consider adding 1 dose of dexamethasone 10 mg; for CRS that develops ≥72 hours after infusion, treat symptomatically. For patients who received idecabtagene or lisocabtagene, consider administering dexamethasone 10 mg IV every 24 hours for early-onset CRS (<72 hours after infusion). Additional supportive care for Grade 1 CRS includes sepsis screen and empiric broad spectrum antibiotics (especially in neutropenic patients), judicious use of IV fluids, electrolyte repletion, and management of specific organ toxicities.

Grade 2 (fever with hypotension not requiring vasopressors and/or hypoxia requiring low-flow nasal cannula or blow-by): Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose) is recommended, and can be repeated in 8 hours if no improvement is observed. No more than 3 doses should be administered in 24 hours, with a maximum of 4 doses total. Dexamethasone 10 mg IV every 12-24 hours (or equivalent) can be considered (depending on the product) for persistent refractory hypotension after 1-2 doses of an anti-IL-6 therapy. Note that some centers and manufacturer recommendations suggest the use of corticosteroids routinely for grade 2 CRS. Cardiac monitoring should be performed at least at the onset of grade 2 CRS until resolution to Grade 1 or less. Additional supportive care for Grade 2 CRS includes IV fluid bolus as needed, management as per Grade 3 if no improvement is observed within 24 hours of initiating anti-IL6 therapy, and symptomatic management of organ toxicities. For those with persistent refractory

hypotension after two fluid boluses and anti-IL-6 therapy, clinicians should start vasopressors, transfer the patient to an intensive care unit (ICU), consider an echocardiogram, and initiate more thorough methods of hemodynamic monitoring. Telemetry and electrocardiogram (EKG), along with assessment of troponin and brain natriuretic peptide (BNP) should be done if tachycardia persists.

Grade 3 (fever with hypotension requiring a vasopressor with or without vasopressin or hypoxia requiring high-flow cannula, face mask, nonrebreather mask, or Venturi mask): Anti-IL-6 therapy as per Grade 2 is recommended, if the maximum dose is not reached within a 24-hour period. Dexamethasone 10 mg IV (or equivalent) should be administered every 6 hours. Patient can be managed as Grade 4 if refractory to this treatment. Additional supportive care for Grade 3 CRS includes the transfer of the patient to the ICU, an echocardiogram, hemodynamic monitoring, supplemental oxygen, IV fluid bolus and vasopressors as needed, and symptomatic management of organ toxicities.

Grade 4 (fever with hypotension requiring multiple vasopressors, excluding vasopressin, and/or hypoxia requiring positive pressure [eg, continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), intubation, mechanical ventilation]): Anti-IL-6 therapy as per Grade 2 is recommended, if the maximum dose is not reached within a 24-hour period. Dexamethasone 10 mg IV (or equivalent) should be administered every 6 hours. If refractory, 3 doses of methylprednisolone 1000 mg/day IV can be considered; dosing every 12 hours can also be considered. For example, methylprednisolone IV 1000 mg/day can be administered for 3 days, followed by a rapid taper at 250 mg every 12 hours for 2 days, 125 mg every 12 hours for 2 days, and 60 mg every 12 hours for 2 days. Other agents such as anakinra, siltuximab, ruxolitinib, cyclophosphamide, IVIG, ATG, or extracorporeal cytokine adsorption with CRRT might also be considered.

Tocilizumab availability may be limited due to the FDA Emergency Use Authorization for hospitalized patients with severe COVID-19.[349] Under these conditions, the NCCN panel recommends that the use of tocilizumab be limited to a maximum of 2 doses during a CRS episode. Clinicians should also consider using steroids more aggressively (eg, with the first or second dose of tocilizumab). If necessary, replacement of the second dose of tocilizumab with siltuximab or anakinra can be considered, although again there is limited evidence to support this approach and neither of these agents have received FDA approval for the treatment of CRS.

Neurotoxicity

Neurotoxicity is another adverse event that commonly occurs with CAR T-cell therapies. As with CRS rates, neurotoxicity incidence rates following CAR T-cell therapy reported in clinical trials vary widely, and is due to many factors, including differences in grading scales, CAR design and development, and clinical trial design. The rates of CAR T-cell-related neurotoxicity can vary across products, and clinicians should familiarize themselves with their frequency for the product(s) they are using.

Presentation and onset

The neurotoxicity that occurs with CAR T-cell therapies has been termed Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS) by the ASTCT, and is defined as a disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells.[316]

Occasionally, neurological adverse events may occur in the context of CRS, especially headaches. Neurological symptoms due to CRS typically happen earlier than ICANS and lack the more generalized encephalopathy and frequent language disturbances of the latter. It is

very important to remember that ICANS, unlike CRS, is generally unresponsive to tocilizumab, which is unable to cross the BBB when administered intravenously.[320,350,351] Data from a preclinical study showed that prophylactic treatment with tocilizumab did not prevent CAR T-cell induced neurotoxicity in a mouse model.[321] Similarly, data from a small study in 43 patients who received CD19-directed CAR T-cell therapy suggested that early intervention therapy with tocilizumab did not have an impact on overall neurotoxicity rates or in preventing severe neurotoxicity events.[352] Other studies have also found that tocilizumab did not alleviate neurologic toxicities in patients treated with CD19-directed CAR T-cell therapies.[303,350]

Transient neurological symptoms reported to occur with CAR T-cell therapies can be heterogeneous and include encephalopathy, delirium, aphasia, lethargy, headache, tremor, myoclonus, dizziness, motor dysfunction, ataxia, sleep disorder (eg, insomnia), anxiety, agitation, and signs of psychosis. Serious events, such as seizures, depressed level of consciousness, and fatal and serious cases of cerebral edema, have also occurred. Despite similarities with other encephalopathies, the neurotoxicity associated with CAR T-cell therapy has distinct common features, including language disturbances, encephalopathy, and motor dysfunction, which are captured in the ASTCT consensus grading criteria for ICANS.[316,320,350,353] Headache alone is not considered a useful diagnostic symptom for ICANS, as it is very common and frequently co-occurs with fever. The ASTCT consensus guidelines include intracranial pressure and edema as domains for ICANS grading, but cerebral edema is very rare and it is unclear if it arises from a distinct pathophysiology.[316]

The typical time to onset of neurotoxicity is 4-10 days after receiving CAR T-cell therapy, with a duration of 14-17 days.[308,310-313,320,350,354] The duration may be slightly shorter with BCMA-directed CAR T-cell therapies.[315,355]

Pathophysiology

Although the pathophysiology is not yet fully understood, CAR T-cell-related neurotoxicity is thought to occur as a result of endothelium cell activation and leak in the central nervous system, leading to elevated inflammatory cytokines in the cerebrospinal fluid (CSF).[317,320,342,350,356,357] Several cytokines are implicated in the pathophysiology of CAR T-cell related neurotoxicity, including IL-6, IFNγ, and TNFα.

Risk factors

CRS is considered a strong risk factor for ICANS, with the severity of CRS correlating with that of ICANS.[314,320,350,353,357] Other possible ICANS risk factors may include higher disease burden, high baseline inflammatory state, pre-existing neurologic comorbidities, and higher CAR T-cell dose.[320,342,350] High-grade ICANS is more common with CD19-directed CAR than BCMA-directed CAR.[308-315,355] As with CRS, reported risk factors and incidence vary across studies.[320,350,354,358]

Grading

The NCCN panel recommends following the ASTCT ICANS Consensus grading scale, which consists of an Immune Effector Cell-Associated Encephalopathy (ICE) score as a standardized assessment for encephalopathy, as well as the following four neurologic domains: level of consciousness, seizure, motor findings, and elevated ICP/cerebral edema (see CART-4).[316] The pediatric version incorporated the Cornell Assessment of Pediatric Delirium (CAPD) score in place of ICE assessment in children younger than 12 years or those with developmental delay.[316] The overall ICANS grade is the most severe symptom in any of the five domains.

By including only the most common and specific neurotoxicity symptoms that would trigger specific interventions, the ASTCT ICANS consensus grading scale improves the ease of grading compared to the method used by earlier trials, which was to grade by CTCAE multiple individual and often overlapping terms (such as encephalopathy and delirium). For seizures, the ASTCT ICANS grading scale considers any single clinical or subclinical electrographic seizure of any type to be a Grade 3 event, with prolonged or repetitive clinical or subclinical seizures without a return to baseline in between to be Grade 4.

The ICE component of the ASTCT ICANS grading scale is derived from a 10-point screening tool that enables the objective grading of overlapping encephalopathy terms.[316] ICE is a modified version of the CARTOX-10 screening tool, and evaluates the following abilities: 1) orientation, 2) naming, 3) command following, 4) writing, and 5) attention (see CART-4). In addition to contributing to the grade of ICANS, the ICE assessment can be used daily or every shift as a screen for the onset of ICANS during the at-risk period.

Please refer to CART-4 for additional details on use of the ICE screening tool and the ASTCT ICANS grading scale.

Management of ICANS/Neurotoxicities Related to CAR T-cell Therapy

Corticosteroids form the cornerstone of ICANS management, in addition to careful monitoring and supportive care. Tocilizumab is not recommended by the NCCN panel to treat neurotoxicity in patients treated with CAR T-cell therapies, unless there is concurrent CRS. It may be preferable to use corticosteroids alone in the patient with grade 1 CRS (fever alone) and higher grade ICANS due to the possibility that tocilizumab may exacerbate ICANS.

NCCN Recommendations

The panel recommends that clinicians use the ASTCT ICANS Consensus Grading Scale for Adults to grade any CAR T-cell-related neurotoxicity (see CART-4). The ICANS grade is determined by the most severe event (ie, ICE score, level of consciousness, seizure, motor findings, raised intracranial pressure (ICP)/cerebral edema) that is not attributable to any other cause (eg, sedating medication). The ICE score should be derived from the ICE Assessment Tool. This tool can be used to track a patient's status over time; however, clinical judgement is still necessary when using the ICE assessment. 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.

Neurology consultation is recommended at the first sign of neurotoxicity. Upon a neurotoxicity diagnosis, neurologic assessment and grading should be performed 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) is recommended for those with neurotoxicity that is Grade 2 or higher. An electroencephalogram (EEG) for seizure activity should also be conducted for those patients. Clinicians should be cautious when prescribing medications that can cause CNS depression (excluding those needed for seizure prophylaxis or treatment). If dexamethasone is used for prophylaxis of CRS, there may be an increased risk of Grade 4 and prolonged neurologic toxicities.[262,341]

Treatment for neurotoxicity is based on ICANS grade (see CART-5). Supportive care alone is recommended for Grade 1 neurotoxicity. If ICANS develops within 72 hours after infusion of either lisocabtagene maraleucel or idecabtagene vicleucel, consider administering dexamethasone 10 mg IV every 12-24 hours for 2 doses and reassess.

For Grade 2 neurotoxicity, patients should receive supportive care and a dose of dexamethasone 10 mg IV, followed by reassessment. Dexamethasone may be repeated every 6-12 hours, if there is no improvement.

Dexamethasone 10 mg IV every 6 hours or methylprednisolone (1 mg/kg IV every 12 hours) is recommended for Grade 3 neurotoxicity; for patients who received axicabtagene ciloleucel or brexucabtagene autoleucel, methylprednisolone 1 g daily for 3-5 days may be preferable. High-dose corticosteroids are the recommended treatment option for Grade 4 neurotoxicity. For example, methylprednisolone IV 1000 mg/day (may consider twice a day) for 3 days, followed by rapid taper at 250 mg every 12 hours for 2 days, 125 mg every 12 hours for 2 days, and 60 mg every 12 hours for 2 days. Convulsive status epilepticus should be treated as per institutional guidelines.

Patients with ≥Grade 3 neurotoxicity should receive ICU care. Clinicians should consider repeating neuroimaging (CT or MRI) every 2-3 days if the patient has persistent neurotoxicity that is grade 3 or higher. Patients should also undergo assessment for papilledema or other signs of elevated intracranial pressure. If elevated intracranial pressure is excluded, a diagnostic lumbar puncture may be considered for patients with grade 3-4 neurotoxicity. Antifungal prophylaxis should be strongly considered in patients receiving steroids for the treatment of CRS or neurotoxicity. If steroids are given for the management of ICANS, a fast taper should be used once there is improvement.

Tocilizumab can be used for the treatment of CRS in patients with neurotoxicity and CRS occurring concurrently. It may be preferable to use corticosteroids alone in the patient with grade 1 CRS (fever alone) and concurrent higher grade neurotoxicity due to the possibility that tocilizumab may exacerbate neurotoxicity. Consider transferring the patient to the ICU if the neurotoxicity is associated with CRS that is Grade 2 or higher.

Hemophagocytic lymphohistiocytosis/macrophage-activation syndrome (HLH/MAS)

HLH/MAS can be described as severe immunological syndromes caused by uncontrolled immune activation. This is thought to be the result of hyperactivation of macrophages and lymphocytes, increased production of proinflammatory cytokines, infiltration of lymphocytes and histiocytes in tissues and organs, and immune-mediated multiorgan failure.[331,359-361] Unlike HLH/MAS that occurs due to underlying genetic mutations (referred to as primary HLH/MAS), CAR T-cell therapy-induced HLH/MAS is considered a secondary HLH/MAS, as it is caused by an immune trigger.[360,362] One recent study estimated that HLH/MAS occurs in 3.5% of patients treated with CAR T cell therapy.[363] However, the true incidence of HLH/MAS has been debated, in part due to the close overlap in CRS and HLH/MAS symptoms.[331,362,364]

A clear diagnosis of HLH/MAS following CAR T-cell therapy can be difficult, as the clinical features and laboratory abnormalities can have substantial overlap with CRS (eg, high fevers, increased ferritin levels).[316,319,331,365,366] Most patients with moderate to severe CRS have laboratory abnormalities that meet the classic criteria for HLH, such as elevated CRP, hyperferritinemia, cytopenias, hypofibrinogenemia, coagulopathy, and elevated levels of several serum cytokines, including IL-6, INFγ, sIL-2Ra, and GM-CSF.[319,360] Clinical features associated with CAR T-cell induced HLH include fever, multiorgan dysfunction, and CNS issues (eg, headaches, vision disturbances, and issues related to walking), but patients may not have hepatosplenomegaly or evidence of hemophagocytosis.[316,331,359]

Because HLH/MAS symptoms resolve with the clinical management and resolution of CRS in most cases (and therefore there is no need to

directly treat HLH/MAS), an expert panel convened by the ASTCT decided to exclude HLH/MAS from the definition of CRS.[316] Furthermore, a separate grading scale for HLH/MAS was not established, due to the degree of similarity with CRS and the lack of available CTCAE terms. Clinical management of HLH/MAS mirrors the strategies used for managing CRS, which consists of anti-IL-6 therapy and aggressive use of corticosteroids; the overall goal of this strategy is to suppress the overactive immune cells responsible for the symptoms.[331] A high mortality rate has been linked with refractory HLH/MAS,[367,368] and therefore prompt treatment is required. Some cases of late-onset HLH/MAS-like pathology may occur, which may be tocilizumab refractory. For these cases, corticosteroids and anakinra should be considered. There have been anecdotal reports of the resolution of HLH with anakinra administration.[363,369,370] As a last resort, etoposide may be an option for HLH/MAS that shows no improvement with these measures; this is primarily based on clinical experience with non-CAR T-cell associated HLH. [331,360,361,367,371] In general, this approach is not recommended due to etoposide's toxicity to T lymphocytes and lack of data in the CAR T-cell setting. Intrathecal cytarabine is another potential option for patients with HLH-associated neurotoxicity,[331] however, data supporting use of this agent in this setting is lacking.

NCCN Recommendations

The NCCN panel recommends the following criteria for when there is clinical concern for HLH/MAS: 1) Rapidly rising and high ferritin (>5000 ng/mL) with cytopenias in the context of fever, especially if accompanied by any of the following: Grade ≥3 increase in serum bilirubin, aspartate aminotransferase (AST), alanine transaminase (ALT); Grade ≥3 oliguria or increase in serum creatinine; or grade ≥3 pulmonary edema; 2) presence of hemaphagocytosis in bone marrow or organs based on histopathologic assessment of cell morphology and/or CD68 immunohistochemistry (IHC).

For HLH/MAS, treat as per CRS with tocilizumab and steroids, although the suspicion of HLH/MAS should prompt consideration of higher doses of steroids at a given CRS grade. If no improvement is observed within 48 hours, consider addition of anakinra to corticosteroids. Etoposide or intrathecal cytarabine can be considered as a last resort for HLH with CNS involvement.

Hypogammaglobulinemia

Hypogammaglobulinemia is another potential risk associated with CAR T-cell therapy, and has been reported in up to 53% of patients who received CAR T-cell therapy in registrational clinical trials.[262-266]

Characterized by low antibody levels in the blood and an increased risk of infection,[372] hypogammaglobulinemia is a consequence of extremely low B-cell or plasma cell counts, referred to as B-cell or plasma cell aplasia, respectively. These types of aplasia are an expected result of the on-target/off-tumor activity associated with the successful use of CAR T cell therapy, due to the presence of the targeted antigens on non-malignant B cells or plasma cells.[257,362]

Long-term hypogammaglobulinemia can occur, and even in patients with a complete remission after CAR T-cell therapy infusion. Hypogammaglobulinemia may be treated with the infusion of IVIG, a fractionated blood product derived from the plasma of thousands of individuals and contains antibodies against a wide range of pathogens.[373,374] However, at present there is no compelling data for the use of IVIG post CAR T-cell infusion in patients who do not experience frequent or severe infections with hypogammaglobulinemia, and institutional practices vary.

NCCN recommendations

After anti-CD19 CAR T-cell therapy, consider monthly 400-500 mg/kg IVIG replacement for select patients with hypogammaglobulinemia

(those with serum IgG levels <400-600 mg/dL AND serious or recurrent infections [particularly bacterial]). IVIG should be continued until serum IgG levels normalize and infections are resolved. The optimal IgG threshold to use may depend on patient characteristics and infection frequency or severity.

Hematological Toxicities

Patients who receive CAR T-cell therapy are also at risk of hematological toxicities, including prolonged cytopenia, such as neutropenia, thrombocytopenia, anemia, and/or leukopenia.

Acute cytopenia is common in patients treated with CAR T-cell therapy; however, Grade 3 or higher prolonged cytopenia that remained unresolved weeks or months after infusion are reported frequently in patients treated with CAR T-cell therapies.[262-266] Clinicians should be aware that cytopenia may occur in the weeks to months following lymphodepleting chemotherapy and CAR T-cell therapy infusion.

Factors that may contribute to prolonged cytopenias include CRS and ICANS severity, disease burden, the number of prior therapies, baseline blood cell counts, peak CRP and ferritin levels, and CAR construct.[318,375,376] Although lymphodepletion may be a contributing factor, the pathophysiology of prolonged cytopenia following CAR T-cell infusion remains unclear.[377]

Cytopenias are generally managed with transfusion or growth factor support, if the possibility of myelodysplastic syndrome has been ruled out.[359,378,379] Growth factors may be considered for persistent cytopenias. The guidelines do not provide specific recommendations on the management of CAR T-cell therapy-associated cytopenia in the current version of the guidelines.

Infections

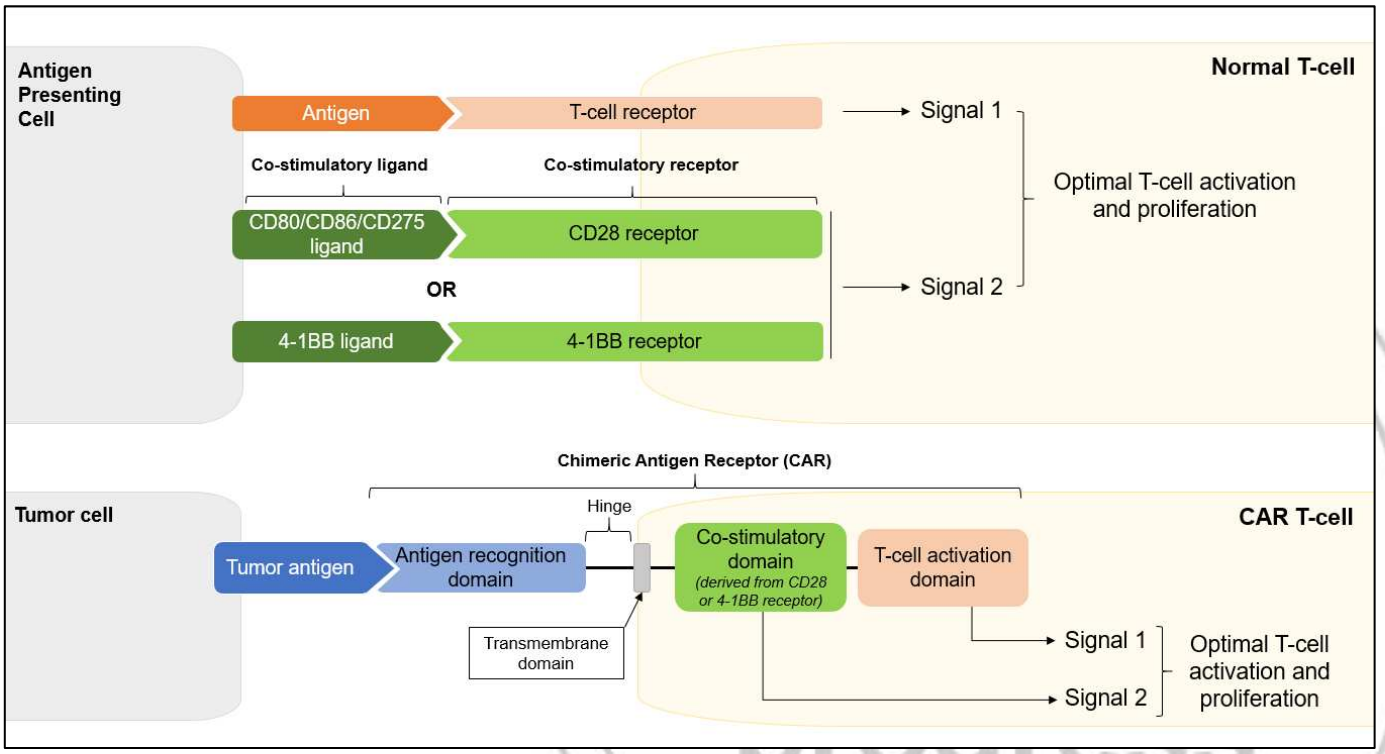
Infections following CAR T-cell therapy are common, and have been reported in up to 70% of patients who received a CAR T-cell therapy in registrational clinical trials for approved agents.[262-266] Bacterial, viral, and fungal infections have all been reported with use of CAR T-cell therapy.[380,381] Most infections occur soon after infusion and may occur for a number of reasons, including lymphodeleting or antecedent chemotherapy, CAR T-cell mediated B-cell or plasma cell depletion, prolonged cytopenias, corticosteroid treatment, or as a consequence of the malignancy itself.[359,382] The severity of CRS may also be associated with an increased risk of acute infections.[380-382] Other potential risk factors for severe infections within the first 30 days include ICANS, tocilizumab and corticosteroid use.[377] Patients remain at increased risk of complications for weeks to months after infusion.[314,380,383,384] Infections are generally managed using agents that target the source of infection. Additionally, prophylaxis against vesicular stomatitis virus (VSV)/herpes simplex virus (HSV) reactivation and *Pneumocystis jirovecii* pneumonia (PJP) infections is generally used for patients undergoing CAR T-cell therapy and for several months following. The decision to administer antibacterial or antifungal prophylaxis should be risk-adjusted based on patient characteristics, such as prior lines of suppressive therapy, infection history, etc.[385] IVIG replacement therapy may be used for select patients. The guidelines recommend IVIG replacement for certain patients treated with anti-CD19 CAR T-cell therapy who experience serious or recurrent infections (particularly bacterial) concurrently with hypogammaglobulinemia. For additional guidance on infections and vaccinations, please refer to the NCCN Guidelines on the Prevention and Treatment of Cancer-Related Infections.

Summary: CAR T-cell Therapy

CAR T-cell therapies are a novel and revolutionary class of cancer therapies that have demonstrated efficacy against several types of

cancers. However, data from clinical trials have shown that all approved CAR T-cell therapies are associated with unique adverse reactions, including CRS and neurologic toxicities. Patient monitoring before, during and after CAR T-cell therapy is critical for early recognition of potential toxicities and timely intervention. CAR T-cell related toxicities can generally be reversed through the use of appropriate management strategies, such as immunosuppressive agents. Due to the changing therapeutic landscape, recommendations for management of CAR T-cell toxicities will continue to evolve as data emerge from clinical trials evaluating novel treatment options.

Figure 1: Optimal T-cell (and CAR T-cell) activity requires two signals



(Top) For the full activation and proliferation of T-cells, two signals are required. Signal 1 results from the interaction between the peptide antigen expressed on the antigen presenting cell (APC) and the T-cell receptor. Signal 2 results from the interaction between a co-stimulatory receptor (such as CD28 or 4-1BB) expressed on T-cells and its corresponding ligand expressed on APCs.

(Bottom) Chimeric antigen receptors are modular structures comprised of an antigen recognition domain, a hinge domain, a transmembrane domain, and at least 1 intracellular domain. Intracellular domains of currently available CAR T-cells include a co-stimulatory domain (derived from CD28 or 4-1BB) and a T-cell activation domain. Incorporation of both types of intracellular domains in a single construct is thought to enable CARs to transduce both Signal 1 and Signal 2 upon binding to the tumor antigen, thereby enhancing the activation and proliferation of CAR T-cells.

Please note that the schematic is not drawn to scale. Refer to the text for references.

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