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Immune-Related Adverse Events (irAEs) Associated with Immune Checkpoint Inhibitors
# Table of Contents

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- irAEs Associated with ICPIs
- Diagnosis, Management, and Monitoring of irAEs
- Specific Management of irAEs
- Additional Resources for Management of irAEs
Overview of Immune Checkpoint Inhibitors (ICPIs)
Overview of ICPIs

Immune Checkpoints: Definition

- **Immune checkpoint** molecules are key modulators of the anti-tumour T cell immune response. They are present on T cells, antigen-presenting cells (APCs) and tumor cells; the receptor-ligand binding interaction activates either inhibitory or activating immune signaling pathways\(^1\).

**Inhibitory immune checkpoints\(^1\):**

- **Induce negative** signal to T cells
- Vital role maintaining immune self-tolerance
  - Prevent T cells from showing autoimmune reactions
- **Examples:**
  - Cytotoxic T-lymphocyte antigen 4 (CTLA-4)
  - Programmed cell death protein 1 (PD-1)
  - Programmed cell death protein ligand 1 (PD-L1)
  - Lymphocyte-activation gene 3 (LAG-3)
  - T cell immunoglobulin and mucin domain 3 (TIM-3)
  - V-domain immunoglobulin suppressor of T cell activation (VISTA)

**Co-stimulatory immune checkpoints\(^1\):**

- **Enhance** T cell expansion and survival
- **Examples:**
  - D40
  - OX40
  - 4-1BB
  - Glucocorticoid-induced tumour necrosis factor (TNF) receptor (GITR)
  - Inducible T cell co-stimulator (ICOS)

CTLA-4 and PD-1 are the best characterized immune-checkpoints\(^2\)

Drugs that interact with these checkpoints are available: Immune checkpoint-directed therapies

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Overview of ICPIs

Immune Checkpoints: **CTLA-4 and PD-1 Pathways**

### CTLA-4 Pathway\(^1,2\)
- Active in secondary lymphoid organs
- Controls **priming phase** of T-cell activation
- CTLA-4 displaces CD28 binding of B7-1 and B7-2 to prevent T-cell activation

### PD-1 Pathway\(^1,2\)
- Active in peripheral tissues and secondary lymphoid organs
- Controls **effector phase** of T-cell activation
- Binding PD-L1 to PD-1 suppresses effector T-cell function

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Reprinted from Cancer Cell, Zappasodi et al. Emerging Concepts for Immune Checkpoint Blockade-Based Combination Therapies, 581-98., Copyright (2018), with permission from Elsevier

CD28, cluster of differentiation 28; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; MHC, major histocompatibility complex; PD-1, programmed cell death 1; PD-L1, programmed death ligand 1; TCR, T-cell receptor; Treg, regulatory T cell.

Overview of ICPIs

Immune Checkpoints Inhibitors: **Targets and Drugs**

- **Target CTLA-4 (receptor)**
  - Ipilimumab

- **Target PD-1 (receptor)**
  - Pembrolizumab
  - Nivolumab
  - Cemiplimab
  - Dostarlimab

- **Target PD-L1 (ligand)**
  - Atezolizumab
  - Avelumab
  - Durvalumab

**CTLA-4**, cytotoxic T-lymphocyte-associated protein 4; PD-1, programmed cell death 1; PD-L1, programmed death ligand 1.

Overview of ICPIs

Immune Checkpoints Inhibitors: Mechanism of Action

- ICPIs block immune inhibitory checkpoint pathways releasing the brakes on the immune response\textsuperscript{1,2}

\begin{center}
\includegraphics[width=\textwidth]{icpi_diagram.png}
\end{center}

CD- cluster of differentiation; \textbf{CTLA-4} - cytotoxic T-lymphocyte antigen 4; \textbf{MHC} - major histocompatibility complex; \textbf{PD-1} - programmed cell death protein 1; \textbf{PD-L1} - programmed cell death ligand; \textbf{TCR} - T-cell receptor

\textsuperscript{1} OncologyPro. \textit{ESMO handbook of immuno-oncology}. Accessed April 7, 2020; \textsuperscript{2} Kreamer et al., J Adv Pract Oncol. 2014;5:418-431; \textsuperscript{3} Singh et al. Gastroenterology Report.2015;3(4), 289-297

\textsuperscript{8} The figure is reproduced with the permission of GSK. Singh et al. Gastroenterology Report.2015;3(4), 289-297
Overview of ICPIs

Summary

- Immune checkpoint molecules are key modulators of the anti-tumour T cell immune response
  - CTLA-4 and PD-1 are the best characterized immune-checkpoints
  - Tumor cells express PD-L1 that binds to PD-1 to decrease T cell response
  - ICPIs block immune inhibitory checkpoint pathways releasing the brakes on the immune response
  - FDA approved ICPIs and their targets

<table>
<thead>
<tr>
<th>TARGET: Checkpoint molecule</th>
<th>Mechanism of Action</th>
<th>FDA Approved Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTLA-4</td>
<td>Anti-CTLA-4</td>
<td>Ipilimumab</td>
</tr>
<tr>
<td>PD-1</td>
<td>PD-1 Inhibitors</td>
<td>Pembrolizumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nivolumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cemiplimab</td>
</tr>
<tr>
<td>PD-L1</td>
<td>PD-L1 Inhibitors</td>
<td>Atezolizumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Avelumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Durvalumab</td>
</tr>
</tbody>
</table>

CTLA-4, cytotoxic T-lymphocyte–associated protein 4; PD-1, programmed cell death 1; PD-L1, programmed death ligand 1.
irAEs Associated with ICPIs
irAEs Associated with ICPIs

Pathophysiology

- Pathophysiology underlying irAE is unknown but it is believed to be related to the role that immune checkpoints play in maintaining immunologic homeostasis.¹

irAEs Associated with ICPIs

Onset and Duration

- irAEs associated with ICPIs differ from adverse events of chemotherapy\textsuperscript{1,2}

  - Chemotherapy-related AEs generally occur during treatment, but irAEs can occur at any time\textsuperscript{1,2}
  - irAEs tend to have a delayed onset and longer duration than toxicities related to chemotherapy\textsuperscript{1}
    - Onset of irAEs is variable and differs by organ system and type of therapy\textsuperscript{2}
    - irAEs may even arise months or years after end of treatment with immunotherapy\textsuperscript{1}
  - Relationship between immunotherapy dose/exposure and irAEs is not well understood\textsuperscript{1}

irAEs, immune-related adverse event.
irAEs Associated with ICPIs

Organs Affected

- ICPIs are associated with toxicities caused by **nonspecific immune activation**\(^1\)\(^-\)\(^3\)
- irAEs can target any organ\(^1\)\(^-\)\(^3\)

irAEs are most common in: \(^1\)\(^-\)\(^3\)

- **Skin**
- **Gastrointestinal**
- **Endocrine**

Select Organ Systems and Corresponding irAEs\(^3\)

From NEJM. Postow et al., Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. 378, 158. Copyright © (2018) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

irAEs, immune-related adverse event.
irAEs Associated with ICPIs

Onset and Duration

- Onset of irAEs is variable and differs by organ system and type of therapy
- irAEs may present after treatment discontinuation
- Safety monitoring should extend after therapy ends

Kinetics of irAEs in patients treated with anti-PD-1/PD-L1

The graph is reproduced with the permission of GSK. Martins et al. Nature Rev. 2019;16:565-580

irAEs, immune-related adverse event; PD-1, programmed cell death 1; PD-L1, programmed death ligand
irAEs Associated with ICPIs
Most irAEs Are Mild or Moderate, But Serious irAEs Can Occur

- irAEs (any grade) occur in up to 70% of patients on anti-PD-1/anti-PD-L1 monotherapy\(^a\) and up to 90% of patients on anti–CTLA-4 monotherapy\(^b,1-3\)
- Grade ≥3 irAEs are estimated to occur in 15%–42% of patients on anti–CTLA-4 therapies and ≤10% of patients on anti–PD-1/anti–PD-L1 therapies\(^1-3\)

\(\text{\footnotesize \text{*\textsuperscript{a} patients with advanced cancer; \textsuperscript{b} patients with melanoma \textsuperscript{CTLA-4, cytotoxic T-lymphocyte–associated protein 4; GI, gastrointestinal; irAE, immune-related adverse event; PD-1, programmed cell death 1; PD-L1, programmed death ligand 1.}}\text{\footnotesize }\)}\)


The graph is reproduced with the permission of GSK. Brahmer et al. J Clin Oncol. 2018;36(17):1714-1768.
irAEs Associated with ICPIs

Fatal Toxic Effects with ICI Monotherapy

Systematic Review and Meta-Analysis Assessing Spectrum, Timing and Clinical Characteristics of Fatal ICPI-Associated Toxic Effects*

ICI-related Fatalities due to irAEs Differ Between Regimens:

- **Incidence** of fatal toxicities with ICPI monotherapy was 0.36% to 0.38% with anti-PD-1/PD-L1 therapy and 1.08% with anti-CTLA-4 therapy
- **Colitis** was most frequent cause of anti-CTLA-4 monotherapy fatalities (135 out of 193 [70%])
- **Pneumonitis** (115 out of 333 [35%]) and **hepatitis** (74 out of 333 [22%]) were more frequent causes of anti-PD-1/PD-L1 related fatalities

*Based on retrospective query of World Health Organization (WHO) pharmacovigilance database (Vigilyze) comprising more than 16 000 000 adverse drug reactions, and records from 7 academic centers

Time to Symptom Onset of Fatal Toxic Effects by ICI Regimen

- Fatal toxicities with ICI monotherapy occurred within a **median 40 days** after monotherapy initiation

The graph is reproduced with the permission of GSK. Wang et al. JAMA Oncol. 2018;4(12):1721-8

1: Wang et al. JAMA Oncol. 2018;4(12):1721-8
irAEs Associated with ICPIs

Fatal Toxic Effects with ICI Monotherapy Based on Organ-System

Systematic Review and Meta-Analysis Assessing Spectrum, Timing and Clinical Characteristics of Fatal ICPI-Associated Toxic Effects*

- **Myocarditis** had the highest fatality rate (52 out of 131 cases [39.7%])
- **Endocrine toxic effects** and **colitis** had the lowest fatality rates (2%-5%)

*Based on retrospective query of World Health Organization (WHO) pharmacovigilance database (Vigilyze) comprising more than 16,000,000 adverse drug reactions, and records from 7 academic centers

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1. Wang et al. JAMA Oncol. 2018;4(12):1721-8
irAEs Associated with ICPIs
Common Presentations in Patients Visiting Emergency Department (ED)

- Retrospective review of 628 patients receiving ICPIs who visited ED at MD Anderson Cancer Center (March 2011 to February 2016)
- Of 1026 ED visits, 257 (25.0%) related to ≥1 irAEs; 210 of the 257 (81.7%) of irAE-related ED visits lead to admission
- Diarrhea was the most common adverse events associated with ED visits

<table>
<thead>
<tr>
<th>irAE, %</th>
<th>Ipilimumab (n = 186)</th>
<th>Nivolumab (n = 154)</th>
<th>Pembrolizumab (n = 109)</th>
<th>&gt; 1 Agent (n = 179)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>14.5</td>
<td>8.4</td>
<td>6.4</td>
<td>18.4</td>
</tr>
<tr>
<td>Colitis</td>
<td>7.0</td>
<td>2.6</td>
<td>1.8</td>
<td>7.3</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>3.2</td>
<td>7.1</td>
<td>4.6</td>
<td>4.5</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>4.3</td>
<td>4.5</td>
<td>4.6</td>
<td>7.8</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>4.3</td>
<td>0.6</td>
<td>0</td>
<td>5.0</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>1.1</td>
<td>6.1</td>
<td>1.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>1.6</td>
<td>0.6</td>
<td>0</td>
<td>5.0</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>1.1</td>
<td>1.9</td>
<td>0.9</td>
<td>5.0</td>
</tr>
<tr>
<td>Adrenalitis</td>
<td>0.5</td>
<td>1.3</td>
<td>0</td>
<td>1.1</td>
</tr>
</tbody>
</table>

ICPI, immune checkpoint inhibitor; irAEs, immune-related adverse event.
irAEs Associated with ICPIs

Relationship with Outcomes

- Interplay between irAEs and efficacy of checkpoint inhibitor therapy is not fully understood\(^1\)
  - Some analyses suggest that development of irAEs is associated with increased response to checkpoint inhibitors and improved outcomes\(^2\)
  - Other studies have not observed this effect\(^3\)

- Use of immunosuppressive therapies for management of irAEs does not appear to adversely affect treatment outcomes\(^2-4\)
  - Retrospective studies suggest that use of immunosuppressive therapies does not negatively affect OS, TTF, or ORR\(^2-4\)

ICI, immune checkpoint inhibitor; irAEs, immune-related adverse event; OS, Overall survival; ORR, Overall response rate; TTF, time to treatment failure

irAEs Associated with ICPIs

Resolution

- Most of irAEs are reversible when recognized and managed promptly$^{1-4}$
  - Dose delay/Permanent discontinuation$^{1-4}$
  - Immunomodulation: systemic corticosteroids or suppressive immunomodulating agents$^{1-4}$
- Endocrinopathies are unique because they are often irreversible$^{1,2}$
  - Most common endocrine irAEs: acute hypophysitis and thyroid disease/abnormalities in thyroid function tests (eg, primary hypothyroidism or thyroiditis)
  - However, many endocrine irAEs can be managed with hormone replacement$^4$
irAEs Associated with ICPIs

Summary

- Pathophysiology underlying irAE is **unknown** but it is believed to be related to the role that immune checkpoints play in maintaining immunologic homeostasis\(^1\)
- irAEs associated with ICPIs:
  - **Differ** from adverse events of chemotherapy and tend to have a delayed onset and longer duration than toxicities related to chemotherapy\(^2,3\)
  - Can target **any organ**, most commonly: skin, gastrointestinal and endocrine\(^1,2,4\)
  - **Onset** is **variable** and differs by organ system and type of therapy\(^1\)
  - Incidence can vary among malignancies\(^1\)
  - Most are **reversible** when recognized and managed promptly\(^4-7\)
    - Endocrinopathies are unique because they are often irreversible\(^5,6\)
  - Grade 5/Fatal irAES are **rare**\(^8\)
  - Interplay between irAEs and efficacy of checkpoint inhibitor therapy is **not fully understood**\(^1\)

ICPI, immune checkpoint inhibitor; irAEs, immune-related adverse event.

Diagnosis, Management, and Monitoring of irAEs
Diagnosis and Management of irAEs

Diagnosis and General Management

- Early recognition and prompt intervention are critical to successful management of irAEs.\textsuperscript{1,2}

**Early involvement** of multidisciplinary team: physicians, nurses, pharmacists.\textsuperscript{1,2}

Patient and caregivers **education.**\textsuperscript{1,2}

Consult with **relevant specialty services** (eg, dermatology, endocrinology) in a timely manner.\textsuperscript{1,2}

**Exercise caution,** as any new symptoms that arise may be related to irAEs.\textsuperscript{1,2}

**Dose reductions** of ICPIs are not recommended

Instead, **permanent discontinuation** or **treatment interruption** are recommended, as appropriate.\textsuperscript{1,2}

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ICPI, immune checkpoint inhibitor; irAEs, immune-related adverse event.

Diagnosis and Management of irAEs
severity-guided general management of immune-related adverse events (irAEs) and immunotherapy re-challenge
please refer to the guidelines for specific management of irAEs by organ system

The Figure is reproduced with the permission of GSK. Nakajima EC et al. J Clin Oncol. 2019; 37(30): 2714-2718

a Please see slide 28 for guidelines available on management of irAEs

irAEs, immune-related adverse event.
## Diagnosis and Management of irAEs

### General Management

<table>
<thead>
<tr>
<th>Symptom Grading&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Summary of Management Strategy by Grade (Non-Organ Specific)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Continue therapy with close monitoring</td>
</tr>
<tr>
<td></td>
<td>with exception of some neurologic, hematologic, and cardiac toxicities</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Withhold therapy; consider resuming when symptoms or lab values return to grade ≤1</td>
</tr>
<tr>
<td></td>
<td>• Corticosteroids may be administered</td>
</tr>
<tr>
<td></td>
<td>• Initial dose: 0.5–1.0 mg/kg per day of prednisone or equivalent</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Withhold therapy; begin high-dose corticosteroids</td>
</tr>
<tr>
<td></td>
<td>• Dose: prednisone 1–2 mg/kg per day or methylprednisolone IV 1–2 mg/kg per day</td>
</tr>
<tr>
<td></td>
<td>• Taper corticosteroids over the course of at least 4–6 weeks</td>
</tr>
<tr>
<td></td>
<td>• If symptoms do not improve after 48–72 hours of corticosteroid treatment, consider additional immunosuppressive strategies (eg, infliximab for some toxicities, but never use for hepatitis)</td>
</tr>
<tr>
<td></td>
<td>• Some grade 3 toxicities may require permanent discontinuation</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Usually require permanent discontinuation of therapy</td>
</tr>
<tr>
<td></td>
<td>Endocrinopathies that have been controlled by hormone replacement are an exception and may not require discontinuation</td>
</tr>
</tbody>
</table>

---

<sup>a</sup> Grading of adverse events according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0


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**Therapy withheld due to irAEs may be re-initiated when symptoms and/or laboratory values return to grade ≤1; use caution when re-initiating therapy, particularly in patients with early-onset irAEs**
Diagnosis and Management of irAEs

General Guidance for Corticosteroid Management of irAEs (Non-organ Specific)

Principles of steroid use in the management of irAEs

- Corticosteroids are the mainstay of treatment in the management of irAEs related to immunotherapy
- Early intervention 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 the absence of specific indications such as prior infusion reaction or concurrent chemotherapy, routine premedication with corticosteroids is not recommended given the potential mitigation of immunotherapeutic effectiveness in the prophylactic setting

Steroid dosing

- See individual toxicity pages for specific recommendations on steroid dose by grade.
- For neurologic, cardiac, or grade 3 or 4 irAEs, higher dose of steroids (e.g., methylprednisolone or prednisone 1-2 mg/kg/day) should be given
- Higher potency topical steroids are preferred for short-term use for immune-related dermatitis, compared to longer term use of lower potency steroids

Steroid Taper

- Longer steroid tapers (> 4 weeks, sometimes 6-8 weeks or longer) maybe required to prevent recurrent irAEs, particularly pneumonitis and hepatitis

AE, adverse event; irAEs, immune-related adverse event; IV, intravenous

a - Grading of adverse events according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0

Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Management of Immunotherapy-Related Toxicities.V.1.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed Feb 11, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available.
# Diagnosis and Management of irAEs

## General Guidance for Corticosteroid Management of irAEs (Non-organ Specific)

### Symptom Grading

<table>
<thead>
<tr>
<th>Grade</th>
<th>Corticosteroid Management by Grade</th>
<th>Additional Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>• Corticosteroids not usually indicated</td>
<td>• Continue immunotherapy</td>
</tr>
<tr>
<td></td>
<td>If indicated, start oral prednisone 0.5-1 mg/kg/day if patient can take oral medication.</td>
<td>• Hold immunotherapy during corticosteroid use</td>
</tr>
<tr>
<td></td>
<td>• If IV required, start methylprednisolone 0.5-1 mg/kg/day IV</td>
<td>• Continue immunotherapy once resolved to ≤ grade 1 and off corticosteroids</td>
</tr>
<tr>
<td></td>
<td>• If no improvement in 2–3 days, increase corticosteroid dose to 2 mg/kg/day</td>
<td>• Start proton pump inhibitor for GI prophylaxis</td>
</tr>
<tr>
<td></td>
<td>• Once improved to ≤ grade 1 AE, start 4–6 week steroid taper</td>
<td>• Hold immunotherapy; if symptoms do not improve in 4–6 weeks, discontinue immunotherapy</td>
</tr>
<tr>
<td>Grade 2</td>
<td>• Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone)</td>
<td>• Consider intravenous corticosteroids</td>
</tr>
<tr>
<td></td>
<td>• If no improvement in 2–3 days, add additional/alternative immune suppressant</td>
<td>• Start proton pump inhibitor for GI prophylaxis</td>
</tr>
<tr>
<td></td>
<td>• Once improved to ≤ grade 1, start 4–6-week steroid taper</td>
<td>• Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (&gt;30 mg prednisone or equivalent/day)</td>
</tr>
<tr>
<td></td>
<td>• Provide supportive treatment as needed</td>
<td>• Discontinue immunotherapy</td>
</tr>
<tr>
<td>Grade 3</td>
<td>• Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone)</td>
<td>• Continue intravenous corticosteroids</td>
</tr>
<tr>
<td></td>
<td>• If no improvement in 2–3 days, add additional/alternative immune suppressant, e.g., infliximab</td>
<td>• Start proton pump inhibitor for GI prophylaxis</td>
</tr>
<tr>
<td></td>
<td>• Provide supportive care as needed</td>
<td>• Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (&gt;30 mg prednisone or equivalent/day)</td>
</tr>
</tbody>
</table>

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**Note:** For steroid-refractory cases and/or when steroid sparing is desirable, management should be coordinated with disease specialists

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**AE, adverse event; irAEs, immune-related adverse event; IV, intravenous**

---

## Diagnosis and Management of irAEs

### Guidelines

<table>
<thead>
<tr>
<th>Society</th>
<th>GUIDELINES for MANAGEMENT of ICPIs-associated irAEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Comprehensive Cancer Network (NCCN®)</td>
<td>NCCN Guidelines for Management of Immunotherapy-Related Toxicities. V.1.2021 &lt;br&gt;Available at: nccn.org</td>
</tr>
</tbody>
</table>

ICPI, immune checkpoint inhibitor; irAEs, immune-related adverse event
Diagnosis and Management of irAEs
Patient and Caregivers

Guideline recommendations
Providing ICPI-specific information to patients and caregivers before initiating therapy

Continued patient and caregiver education throughout treatment and survivorship

Education

IO Wallet Card
The ONS Immunotherapy Patient Wallet Card is intended to communicate with healthcare providers who are not involved with a patient’s cancer. Available at: https://www.ons.org/sites/default/files/2019-01/O%20Card%20sided_Vertical.pdf

Patient management

KEY QUESTIONS

- Have you ever received an immune checkpoint inhibitor/immunotherapy?
  - ✓ irAEs can occur after discontinuation of ICPIs
- Do you have an immunotherapy wallet card?
  - ✓ Wallet cards list the type of immunotherapy, key symptoms, and how to notify HCPs
- Do you have an autoimmune condition?
  - ✓ ICPIs may exacerbate preexisting autoimmune conditions

ICPI, immune checkpoint inhibitor; irAEs, immune-related adverse event.
Diagnosis and Management of irAEs

Effective Management of irAEs Requires a Multidisciplinary Care Team

- Because of the broad range of irAEs, multidisciplinary collaboration is critical for management in order to address specific symptoms\(^1,2\)
- Advanced practice providers, including nurse practitioners and physician assistants, play key roles in educating and monitoring patients\(^3\)
- Early engagement of a multidisciplinary care team is critical for early recognition and prompt intervention of irAEs\(^1-3\)
- Patients should be instructed to notify their providers that they are being treated with or have been treated with immunotherapy\(^2\)

HCP, health care provider; irAE, immune-related adverse event.

# Diagnosis and Management of irAEs

## Common irAEs

<table>
<thead>
<tr>
<th>irAE</th>
<th>Signs and Symptoms (may include 1 or more)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pancreatic</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Acute Pancreatitis: epigastric pain, nausea, possible vomiting. Chronic pancreatitis: chronic abdominal pain, deficiency in pancreatic enzyme production with possible malabsorption</td>
</tr>
<tr>
<td><strong>Dermatologic</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Maculopapular rash (eczema-like spongiotic dermatitis) and pruritus; other dermatologic manifestations include lichenoid reactions, psoriasis, acneliform rashes, vitiligo-like lesions, autoimmune skin diseases (e.g., bullous pemphigoid, dermatomyositis, alopecia areata), sarcoidosis or nail and oral mucosal changes</td>
</tr>
<tr>
<td><strong>Diarrhea/colitis</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Diarrhea, abdominal pain, hematochezia, weight loss, fever, vomiting</td>
</tr>
<tr>
<td><strong>Endocrine</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Headaches, visual disturbances, fatigue, altered consciousness, electrolytes imbalance (particularly hyponatremia), anorexia, mood changes</td>
</tr>
<tr>
<td><strong>Hepatic</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Often asymptomatic and diagnosed via routine blood tests</td>
</tr>
</tbody>
</table>
| **Musculoskeletal**<sup>4</sup> | • Inflammatory arthritis - large and/or small joints may be affected, low grade but severe impact on QoL and ADL may occur; Arthralgia has been reported in ~15% patients  
• Other irAEs include polymyalgia-like syndrome, myositis, vasculitis, lupus-like syndromes |

irAEs, immune-related adverse event.

## Diagnosis and Management of irAEs

### Relatively Uncommon irAEs

<table>
<thead>
<tr>
<th>irAE</th>
<th>Signs and Symptoms (may include 1 or more)</th>
</tr>
</thead>
</table>
| **Pulmonary**¹     | • Pneumonitis is the most common pulmonary irAE and is one of the most common causes of ICI-related death  
  – Incidence with Anti-PD-1/PD-L1 and anti-CTLA-4 therapies: <5% (all grade) and 1%–2% (grade ≥3)  
  – Asymptomatic or characterized by shortness of breath, cough, wheezing, chest pain, fatigue, increased need for supplementary oxygen, reduced tolerance for exercise.  
  • Less common irAEs include pleural effusion, pulmonary sarcoidosis, and sarcoid-like granulomatous reactions |
| **Renal**²        | • Renal irAEs are uncommon and are typically asymptomatic, maybe underreported, low grade kidney injury reported in 25%-29% patients.  
  • Most patients with acute kidney injury present with acute interstitial nephritis; symptoms may include oliguria, hematuria, peripheral edema, and anorexia |
| **Nervous System**¹ | • Neurologic irAEs are uncommon (<4% following treatment with anti-CTLA-4, 6% with anti-PD-1, 12% with combination therapy)  
  • Common symptoms are headache and peripheral sensory neuropathy  
  – Rule out CNS progression of cancer, seizures, infection, metabolism changes  
  • In patients who present with headache, assess whether the patient has new confusion, altered behavior, aphasia, seizure-like activity, or short-term memory loss  
  – These symptoms can be indicative of encephalitis, which can be life-threatening |

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Diagnosis and Management of irAEs
Relatively Uncommon irAEs Continued

<table>
<thead>
<tr>
<th>irAE</th>
<th>Signs and Symptoms (may include 1 or more)</th>
</tr>
</thead>
</table>
| **Hematologic**<sup>1-3</sup> | - Relatively uncommon (Anemia: all grades ~11%; grade 3/4 ~5%; Thrombocytopenia: all grades ~8%; grade 3/4 ~4%)  
- Autoimmune hemolytic anemia is the most common hematologic irAE. Other irAEs include acquired thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, aplastic anemia, lymphopenia, immune thrombocytopenia, acquired hemophilia  
- Distinguish active irAEs from temporary changes in laboratory values that may occur with checkpoint inhibitors |
| **Cardiovascular**<sup>1</sup> | - Rare (<0.1% of patients receiving ICIs), but can be rapidly fatal, symptoms include fatigue and weakness with or without more typical cardiac symptoms (arrhythmia, palpitations, chest pain, or signs and symptoms of heart failure).  
- Cardiogenic shock or sudden death may occur in severe cases |
| **Ocular**<sup>1,2</sup> | - Ocular irAEs, predominantly uveitis, are reported in <1% of patients taking ICIs.  
- Advise patients to report new onset of blurred vision, floaters, flashing lights, changes in color vision, eye redness, photophobia or light sensitivity, visual distortion and visual field changes, scotomas, tender eyes or pain on eye movement, eyelid swelling or proptosis, or double vision |
| **Infusion Reactions**<sup>1</sup> | - Severe/life threatening infusion reactions reported in <2% of patients taking ICIs  
- May present with constitutional symptoms: Fever, rigor, pruritus, hypotension, dyspnea, chest discomfort, rash, urticaria, angioedema, wheezing, or tachycardia  
- Anaphylactic reactions are possible |

ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; QoL, quality of life.

## Monitoring of irAEs

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Principles of Routine Monitoring for ICPIs

### Pre-Therapy Assessment

**Clinical**
- Physical examination
- Comprehensive patient history of any autoimmune/organ-specific disease, endocrinopathy, or infectious disease
- Neurologic examination
- Bowel habits (typical frequency/consistency)
- Infectious disease screening (HIV; hepatitis A, B, C) as indicated

**Imaging**
- Cross-sectional imaging
- Brain MRI if indicated

**General bloodwork**
- CBC (with differential if indicated)
- Comprehensive metabolic panel

**Dermatologic**
- Examination of skin and mucosa if history of immune-related skin disorder

**Pancreatic**
- Baseline testing is not required

### Monitoring Frequency

**Clinical**
- Clinical exam at each visit with AE symptom assessment

**Imaging**
- Periodic imaging as indicated

**General bloodwork**
- Repeat prior to each treatment or every 4 weeks during therapy, then in 6-12 weeks or as indicated

**Dermatologic**
- Conduct/repeat as needed based on symptoms

**Pancreatic**
- No routine monitoring needed if asymptomatic

### Evaluation for Abnormal Findings/Symptoms

- Follow-up testing based on findings, symptoms
- Follow-up testing based on imaging findings
- HbA1c for elevated glucose
- Monitor affected BSA and lesion type; photographic documentation. Skin biopsy if indicated.
- Amylase, lipase, and consider abdominal CT with contrast or MRCP for suspected pancreatitis

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* Prior to initiating treatment, counsel patients and caregivers on the warning signs and symptoms of irAEs.

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

AE: adverse events, BSA: body surface area, CBC: cell blood count, CT: computed tomography, HbA1c: hemoglobin A1c test, ICPI: immune checkpoint inhibitor, irAEs, immune-related adverse event; MRCP: magnetic resonance cholangiopancreatography, MRI: magnetic resonance imaging;
# Monitoring of irAEs

NCCN Guidelines®: Principles of Routine Monitoring for ICPIs

<table>
<thead>
<tr>
<th>Pre-Therapy Assessment&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Monitoring Frequency&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Evaluation for Abnormal Findings/Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thyroid</strong>&lt;br&gt;-Thyroid-stimulating hormone (TSH), free thyroxine (T4)**&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Every 4-6 weeks during immunotherapy, then follow-up every 12 weeks as indicated</td>
<td>Total T3 and free T4 if abnormal thyroid function suspected</td>
</tr>
<tr>
<td><strong>Adrenal/Pituitary</strong>&lt;br&gt;-Consider serum cortisol (morning preferred) and thyroid function as above</td>
<td>Repeat prior to each treatment or every 4 weeks during therapy, then follow-up every 6-12 weeks</td>
<td>Luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone (males), estradiol (females), adrenocorticotrophic hormone (ACTH), and serum cortisol</td>
</tr>
<tr>
<td><strong>Pulmonary</strong>&lt;br&gt;-Oxygen saturation (resting and with ambulation)&lt;br&gt;-Consider pulmonary function tests (PFTs) with diffusion for high-risk patients (eg, interstitial lung disease on imaging, COPD, previous suspected treatment-related lung toxicity)</td>
<td>Repeat oxygen saturation tests based on symptoms</td>
<td>Chest CT with contrast to evaluate for pneumonitis, biopsy, or bronchoscopy with bronchoalveolar-lavage (BAL) if needed to exclude other causes</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong>&lt;br&gt;-Consider baseline ECG&lt;br&gt;-Individualized assessment in consultation with cardiology as indicated</td>
<td>Consider periodic testing for those with abnormal baseline or symptoms</td>
<td>Individualized follow-up in consultation with cardiology as indicated</td>
</tr>
<tr>
<td><strong>Musculoskeletal</strong>&lt;br&gt;-Joint examination/functional assessment as needed for patients with pre-existing disease</td>
<td>No routine monitoring needed if asymptomatic</td>
<td>Consider rheumatology referral. Depending on clinical situation, consider C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), or creatine phosphokinase (CPK)</td>
</tr>
</tbody>
</table>

---

<sup>a</sup> Prior to initiating treatment, counsel patients and caregivers on the warning signs and symptoms of irAEs. See Principles of Immunotherapy Patient Education (IMMUNO-B).

<sup>b</sup> For disease specific COVID-19 recommendations, see the NCCN COVID-19 Resource page.

<sup>c</sup> Closer monitoring may be required for patients with combination immunotherapy regimens. Refer to prescribing information for each individual immunotherapy agent for monitoring recommendations.

CT, computed tomography; ECG, electrocardiogram; ICPI, immune checkpoint inhibitor; irAEs, immune-related adverse event.

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Early recognition and prompt intervention are critical to successful management of irAEs\(^1,2\)

- Dose reduction is not a recommended strategy

- Guidelines on management of ICPIs irAEs and patient monitoring during and after ICPIs treatment available from main clinical societies: ASCO, NCCN, SITC, ESMO

- Patient and caregiver education before starting treatment, throughout and during survivorship is crucial
Specific Management of irAEs
Specific Management of irAEs

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Organ System

**Skin**
Maculopapular rash

**Gastrointestinal**
Diarrhea/Colitis, Hepatic, Pancreatic

**Endocrinopathies**
Hyperglycemia, Thyroid, Hypophysitis, adrenal

**Pulmonary**
pneumonitis

Organ System

**Renal**
Elevated serum creatinine/acute renal failure

**Cardiovascular** (Myocarditis, pericarditis, arrhythmias, impaired ventricular function, conduction abnormalities)

**Musculoskeletal**
Inflammatory arthritis

**Non-specific ICI-related Toxicities**

**Fatigue**
## Specific Management of irAEs

### Skin

| Presentation¹ | - Most commonly presents as rash/inflammatory dermatitis and pruritus  
- Less common: lichenoid, eczematous, bullous dermatitis, and psoriasis |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence¹</td>
<td>Anti-PD-1/PD-L1: 30-40%</td>
</tr>
<tr>
<td></td>
<td>Anti-CTLA-4: ~50%</td>
</tr>
<tr>
<td>Onset¹</td>
<td>Typically arise days or weeks after initiation of therapy, but can occur later</td>
</tr>
</tbody>
</table>
| Overview¹,²    | - Generally low grade and transient but can affect quality of life.  
- Potentially fatal exfoliative dermatologic conditions can occur (eg, Steven Johnson Syndrome/Toxic Epidermal Necrosis (SJS/TEN), drug rash with eosinophilia and systemic symptoms (DRESS))  
- Permanent discontinuation recommended for SJS/TEN or DRESS syndrome |

CTLA-4, cytotoxic T-lymphocyte–associated protein 4; irAEs, immune-related adverse event.  
PD-1, programmed cell death 1; PD-L1, programmed death ligand 1.  
# Specific Management of irAEs

## Skin: Maculopapular Rash

### Assessment/Grading

- Total body skin exam, including mucosa
- Assess for history of prior inflammatory dermatologic diseases
- Consider biopsy if unusual features

### Symptom Grade

<table>
<thead>
<tr>
<th>Grade</th>
<th>Management</th>
</tr>
</thead>
</table>
| Mild (G1)<sup>b</sup> | Continue immunotherapy  
Topical emollient  
Oral antihistamine for pruritus  
Treatment with moderate potency topical steroids to affected areas |
| Moderate (G2)<sup>c</sup> | Continue immunotherapy  
Topical emollient  
Oral antihistamine for pruritus  
Treatment with moderate to high potency topical steroids to affected areas  
If unresponsive to topical, consider prednisone 0.5 mg/kg/day |
| Severe (G3-4)<sup>d</sup> | Hold immunotherapy  
Treatment with high potency topical steroids to affected areas  
Prednisone 0.5-1 mg/kg/day<sup>0</sup> (Increase dose up to 2 mg/kg/day if no improvement)  
Urgent dermatology consultation, consider biopsy  
Consider inpatient care |

### Footnotes in Next Slide

Grade, grade; irAEs, immune-related adverse event.

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Specific Management of irAEs

Skin: Maculopapular Rash

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 Macules/papules covering <10% body surface area (BSA) with or without symptoms (e.g., pruritus, burning, tightness)
c Macules/papules covering 10%-30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental activities of daily living (iADLs)
d Macules/papules covering >30% BSA with or without symptoms; limiting self-care activities of daily living (ADLs)
g Treat until symptoms improve to Grade≤1 then taper over 4-6 weeks

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Specific Management of irAEs
Gastrointestinal (GI)

**Presentation**
- Most common GI irAE is colitis, characterized by diarrhea, abdominal pain, rectal bleeding, mucus in stool, fever
- Hepatitis is less common and is generally asymptomatic; typically detected on routine liver tests
- Acute pancreatitis is rare

**Incidence**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Anti–PD-1: ≤19%</th>
<th>Anti–CTLA-4: 23%–33%</th>
<th>Anti–PD-1 + anti–CTLA-4: ~44%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colitis</td>
<td>Anti–PD-1: ~5%</td>
<td>Anti–CTLA-4: &lt;4%–15%</td>
<td>Anti–PD-1 + anti–CTLA-4: ~30%</td>
</tr>
<tr>
<td>Hepatitis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Onset**
- Diarrhea usually arises after an average of 3 infusions; may recur and can mimic inflammatory bowel disease
- Hepatitis generally arises 6–14 weeks after start of therapy

CTLA-4, cytotoxic T-lymphocyte–associated protein 4; irAEs, immune-related adverse event.
PD-1, programmed cell death 1; PD-L1, programmed death ligand 1.

## Specific Management of irAEs

### Gastrointestinal: Diarrhea/Colitis\(^a\)

<table>
<thead>
<tr>
<th>Symptom Grade</th>
<th>Management</th>
</tr>
</thead>
</table>
| Mild (G1)\(^d\) | Consider holding immunotherapy  
Loperamide or diphenoxylate/atropine for 2-3 days; if no improvement and not done already, obtain labs for infectious workup  
Hydration  
Close monitoring\(^l\)  
If persistent or progressive symptoms, check lactoferrin/calprotectin\(^k\); if positive, treat as G2(below); if negative and no infection, continue G1 management and add mesalamine, cholestyramine |
| Moderate (G2)\(^e,f\) | Hold immunotherapy  
Prednisone/methylprednisolone (1-2 mg/kg/day)\(^m\)  
No response in 2—3 days, continue steroids, consider adding infliximab\(^n,o,p\) or vedolizumab\(^p\) within 2 weeks\(^q\) |
| Severe (G3-4)\(^g\) | G3: Discontinue anti-CTLA-4; consider resuming anti-PD/PD-L1 after resolution of toxicity  
G4: Permanently discontinue immunotherapy agent responsible for toxicity  
Consider inpatient care for provision of supportive care  
Intravenous methylprednisolone\(^l\) (1-2 mg/kg/day)\(^m\); if no response in 1-2 days, continue steroids, consider adding infliximab\(^n,o,p\) or vedolizumab\(^p,q,r\) |

### Assessment/Grading

- Stool evaluation to rule out infectious etiology\(^b\)
  - Nucleic acid amplification tests (NAATs) for GI pathogens/bacterial culture
  - C. difficile
  - Ova and parasites; molecular testing for Giardia and Cryptosporidium spp and E. histolytica; consider microsporidia, Cyclospora/isospora spp
  - Viral pathogens testing when available
  - Based on institutional availability, consider lactoferrin/calprotectin\(^k\)
- Infectious disease screening (HIV; hepatitis A, B, C) as clinically indicated
- Consider abdominal/pelvic CT with contrast if G2-G4 colitis\(^a\)
- Consider GI consultation if G2-G4
  - Colonoscopy or flexible sigmoidoscopy +/- esophagastroduodenoscopy with biopsy\(^c\)

### Footnotes in Later Slide

CT: computed tomography; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; Grade, grade; irAEs, immune-related adverse event; PD-1, programmed cell death 1; PD-L1, programmed death ligand 1.

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## Specific Management of irAEs

### Gastrointestinal: Hepatic irAEs

**Elevated Transaminitis**

**Assessment/Grading**

<table>
<thead>
<tr>
<th>Symptom Grade</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (G1) &lt;3 x ULN</td>
<td>Consider holding immunotherapy for concerning lab value trend Assess transaminases and bilirubin with increased frequency</td>
</tr>
<tr>
<td>Moderate (G2) 3-5 ULN</td>
<td>Hold immunotherapy Monitor liver enzymes/liver function tests (LFTs) every 3-5 days Consider prednisone 0.5-1 mg/kg/day</td>
</tr>
<tr>
<td>Sever (G3) &gt;5-20 ULN</td>
<td>Hold immunotherapy Initiate prednisone 1-2 mg/kg/day If steroid refractory or no improvement after 3 days, consider adding mycophenolate Consider inpatient care Monitor liver enzymes every 1-5 days depending upon magnitude and rate of change Hepatology consultation Infliximab should not be used for hepatitis</td>
</tr>
<tr>
<td>Life-threatening (G4) &gt;20 x ULN</td>
<td>Permanently discontinue immunotherapy Initiate prednisone/methylprednisolone 1-2 mg/kg/day If steroid refractory or no improvement after 3 days, consider adding mycophenolate Inpatient care Monitor liver enzymes daily Hepatology consultation Consider liver biopsy if no contraindications Infliximab should not be used for hepatitis</td>
</tr>
</tbody>
</table>

- **Rule out viral etiology**, disease-related hepatic dysfunction, other drug-induced transaminase elevations
- **Consider GI evaluation**
- **Abdominal ultrasound**
- **Limit/discontinue hepatotoxic medications** (assess acetaminophen, dietary supplement, and alcohol use)

### Assessment/Grading

- **Rule out viral etiology**, disease-related hepatic dysfunction, other drug-induced transaminase elevations
- **Consider GI evaluation**
- **Abdominal ultrasound**
- **Limit/discontinue hepatotoxic medications** (assess acetaminophen, dietary supplement, and alcohol use)

**Footnotes in Later Slide**

*Grade, grade; irAEs, immune-related adverse event; ULN, upper limit of normal*

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## Specific Management of irAEs
### Gastrointestinal: Hepatic irAEs

**Grade>1 transaminitis\(^s\) with elevated bilirubin (unless Gilbert’s syndrome)**

<table>
<thead>
<tr>
<th>Assessment/Grading</th>
<th>Symptom Grade</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Rule out viral etiology, disease-related hepatic dysfunction, other drug-induced transaminase elevations</td>
<td>Bilirubin 1-2 x ULN</td>
<td>Hold immunotherapy</td>
</tr>
<tr>
<td>• Consider GI/hepatology evaluation</td>
<td>Bilirubin 3-4 x ULN</td>
<td>Permanently discontinue immunotherapy</td>
</tr>
<tr>
<td>• Limit/discontinue hepatotoxic medications (assess acetaminophen, dietary supplement, and alcohol use)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Consider abdominal imaging for symptomatic patients to rule out complications</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Footnotes in Later Slide**

irAEs, immune-related adverse event; ULN, upper limit of normal

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# Specific Management of irAEs

## Gastrointestinal: Pancreatic irAEs

### Elevation in amylase/lipase (asymptomatic)

<table>
<thead>
<tr>
<th>Assessment/Grading</th>
<th>Symptom Grade</th>
<th>Management</th>
</tr>
</thead>
</table>
| • Assess for signs/symptoms of pancreatitis<sup>a</sup> | Mild  
≤3 x ULN amylase and/or ≤3 x ULN lipase | If isolated elevation of enzymes without evidence of pancreatitis, **continue immunotherapy**  
Evaluate for pancreatitis (next slide); If evidence of pancreatitis, manage according to pancreatitis algorithm  
Consider other causes for elevated amylase/lipase<sup>bb</sup> |
| • If clinical concern for pancreatitis see acute pancreatitis (next slide) | Moderate  
>3-5 x ULN amylase and/or >3-5 x ULN lipase | If isolated elevation of enzymes without evidence of pancreatitis, **consider continuing immunotherapy**  
Evaluate for pancreatitis: clinical assessment<sup>c</sup>, if persistent moderate to severe amylase and/or lipase elevation, abdominal CT with contrast or MRCP  
Consider other causes for elevated amylase/lipase<sup>bb</sup>  
If evidence of pancreatitis, manage according to pancreatitis algorithm |
| | Severe  
>5 x ULN amylase and/or >5 x ULN amylase | |

---

<sup>a</sup> irAEs, immune-related adverse event; ULN, upper limit of normal

<sup>b</sup> Adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Management of Immunotherapy-Related Toxicities. V.1.2021. © 2021 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available.
Specific Management of irAEs
Gastrointestinal: Pancreatic irAEs

Acute Pancreatitis

<table>
<thead>
<tr>
<th>Assessment/Grading</th>
<th>Symptom Grade</th>
<th>Management</th>
</tr>
</thead>
</table>
| • Assess for signs/symptoms of pancreatitis | Mild (G1)<sup>ff</sup> | Consider holding immunotherapy  
Consider gastroenterology referral  
Intravenous hydration  
Manage as per elevation in amylase/lipase (asymptomatic) (previous slide) |
| • Abdominal CT with contrast | Moderate (G2)<sup>gg</sup> | Hold immunotherapy  
Prednisone/methylprednisolone 0.5-1 mg/kg/day<sup>ii</sup>  
Intravenous hydration |
| • Consider magnetic resonance cholangiopancreatography (MRCP) if clinical suspicion of pancreatitis and no radiologic evidence on CT | Severe (G3-4)<sup>hh</sup> | Permanently discontinue immunotherapy  
Prednisone/methylprednisolone 1-2 mg/kg/day<sup>ii</sup>  
Intravenous hydration |

Footnotes in Later Slide
CT, computed tomography; G, grade; irAEs, immune-related adverse event.

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Specific Management of irAEs

Gastrointestinal irAEs

- Symptoms include: watery diarrhea, cramping, urgency, abdominal pain, blood and mucus in stool, fever, nocturnal bowel movements. Blood in stool and/or fever should prompt a more thorough workup for infection and for other causes of GI bleeding, including peptic ulcer and malignant bleeding.
- It is not necessary to wait for test results before providing therapy to manage irAEs.
- If positive lactoferrin, strongly recommend early endoscopy or flexible sigmoidoscopy with biopsy within first 2 weeks of the onset of symptoms.
- Check calprotectin every 2 months to monitor trend and guide treatment. Stop treatment upon return to normal/negative.
- Fewer than 4 bowel movements above baseline per day and no colitis symptoms.
- 4-6 bowel movements above baseline per day, colitis symptoms, not interfering with activities of daily living (ADLs).
- IV steroid is preferred due to possible absorption impairment.
- More than 6 bowel movements above baseline per day, colitis symptoms, interfering with ADLs, hemodynamic instability, hospitalization, other serious complications (e.g., ischemic bowel, perforation, toxic mega-colic).
- If progressive, consider stool evaluation to rule out infectious etiology.
- Consider endoscopy exam if either lactoferrin or calprotectin is positive.
- Convert to prednisone when appropriate.
- Treat until symptoms improve to Grade≤1 then taper over < 4-6 weeks. In cases where infliximab or vedolizumab is used, an attempt to taper steroids in < 2-4 weeks should be made to minimize the complication of infection.
- Duration of therapy with tumor necrosis alpha (TNF-alpha) blockers or integrin blocker is not clearly defined; evidence supports up to three doses (at weeks 0, 2, and 6) and is associated with reduced recurrence rates. Repeat endoscopy to assess endoscopic healing may be helpful to guide colitis treatment duration but is optional.
- An FDA-approved biosimilar is an appropriate substitute for infliximab.
- Obtain TB test before receiving first dose of infliximab or vedolizumab. Treatment does not need to be held for results.
Specific Management of irAEs

Gastrointestinal irAEs


r Fecal transplantation may be considered for immunosuppressant refractory colitis based on institutional availability and expertise.

s Elevated alanine transaminase (ALT) and aspartate transaminase (AST).

t Consider initiating steroids while waiting for results in case of life-threatening transaminitis.

u Viral etiology may include hepatitis A/B/C/E; CMV; EBV; HSV, VZV; HIV.

v Laboratory tests to consider include ceruloplasmin, alpha-1-antitrypsin, ferritin, ANA titer, mitochondrial Ab M2, smooth muscle Ab, liver/kidney microsome type 1 Ab, IgG, IgM, tissue transglutaminase IgA and IgG, TSH, iron, transferrin.

w When liver enzymes show sustained improvement or return to G≤1, initiate steroid tapering and continue to taper over at least 1 month with frequent follow-up to guide taper duration. Re-escalate as needed.

x Consider early concomitant use of mycophenolate with the initiation of steroids.

y Mycophenolate mofetil treatment (0.5-1 g every 12 hours) can be considered in patients who have persistent severe hepatitis despite high-dose corticosteroids. When LFTs improve to grade 1 or less after completion of a steroid taper, consider discontinuation of mycophenolate at the same time.

z AST, ALT, bilirubin, CMV, CBC, and coagulation factors.

aa Mild symptoms of pancreatitis can include: nausea, bloating, belching, abdominal pain, or back pain.

bb Inflammatory bowel disease, irritable bowel syndrome, bowel obstruction, gastroparesis, nausea/vomiting, medications, alcohol, and/or diabetes mellitus.

cc 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)

dd No requirement for routine monitoring of potential pancreatitis with imaging

ee Provide standard medical care for signs and symptoms of acute pancreatitis, including hospital admission, aggressive fluid resuscitation, and pain control.

ff Any one of the following features present: elevation of amylase/lipase >3 x ULN +/- radiologic findings on CT +/- clinical finding concerning pancreatitis
gg Two of three of the following features present: elevation of amylase/lipase > 3 ULN or radiologic findings on CT or clinical findings concerning for pancreatitis.

hh Elevation of amylase/lipase +/- radiologic findings on CT +/- severe abdominal pain or vomiting and hemodynamically unstable.

ii Evaluate for signs/symptoms of pancreatic exocrine insufficiency and/or diabetes mellitus, and supplement if needed. Follow-up over time to monitor for pancreatic insufficiency.

jj Treat until symptoms improve to Grade ≤1 then taper over 4-6 weeks.
Specific Management of irAEs

Endocrinopathies

**Presentation**

- Most common endocrine irAEs: acute hypophysitis and thyroid disease/abnormalities in thyroid function tests (e.g., primary hypothyroidism or thyroiditis)
  - Less common: primary adrenal insufficiency, diabetes mellitus, hypercalcemia, and hypoparathyroidism
- Patients generally report nonspecific symptoms, such as headache, fatigue, anorexia, and nausea
  - Hormonal changes in patients with cancer complicate identification of endocrine irAEs
  - Diagnosis is further complicated by use of corticosteroids to treat irAEs
  - Maintain a high level of suspicion for endocrine irAEs when there is no alternate explanation for symptoms and initiate workup for endocrine irAEs promptly

**Incidence**

Endocrine irAEs (all grade) reported in ~5%–10% of patients

**Onset**

- Typically expected to arise after 6th or 7th week of treatment
Specific Management of irAEs

Endocrine: Hyperglycemia

**Diagnosis/Workup**

- New-onset hyperglycemia <200 mg/dL AND/OR
- History of type II DM with low suspicion for DKA gauge

- Steroid-related hyperglycemia OR
- Preexisting type II DM

**Management**

- Continue immunotherapy
  - Monitor serial blood glucose with each dose
  - Diet and lifestyle modification if needed, medical therapy per institutional guidelines
  - Consider endocrine consultation if patient is symptomatic and/or glucose is persistently uncontrolled

- Hold immunotherapy until DKA resolves
  - Inpatient care
  - Management of DKA as per institutional guidelines

**Hyperglycemia**

- New-onset fasting glucose preferred
  - New-onset fasting glucose >200 mg/dL OR
  - Random blood glucose >250 mg/dL OR
  - History of type II DM with fasting/random glucose >250 mg/dL

**Footnotes**

- anti-GAD, anti-glutamic acid decarboxylase antibody; DM, diabetes mellitus; DKA, diabetic ketoacidosis; irAEs, immune-related adverse event.

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Specific Management of irAEs
Endocrine: Thyroid

**Assessment**

- Monitor TSH, free T4 every 4-6 weeks
  - If TSH elevated, proceed based on TSH levels as follows or repeat TSH, free T4 in 4-6 weeks

**Management**

- TSH between 4 to <10 OR TSH between 4 to <10
  - Patient asymptomatic
  - Normal free T4
  - Continue immunotherapy
    - Continue to monitor thyroid function tests (TFTs)

- Elevated TSH (>10) OR Normal or low TSH
  - Normal free T4
  - Continue immunotherapy
    - Consider levothyroxine

- Low free T4 OR Low free T4
  - See Central hypothyroidism (next slide); exclude recovery from thyroxicosis

---

**Footnotes in Later Slide**

irAEs, immune-related adverse event; T4, Thyroxine; TSH, thyroid stimulating hormone

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Specific Management of irAEs
Endocrine: Thyroid

**Assessment**

- Clinical (overt) primary hypothyroidism
  - Monitor TSH every 4-6 weeks

- Thyrotoxicosis
  - Low or suppressed TSH with high free T4/total T3
  - Consider endocrine consultation if symptomatic

**Management**

- **Continue immunotherapy**
  - Consider endocrine consultation
  - Initiate thyroid hormone supplementation with levothyroxine
  - Repeat TSH in 4-6 weeks to guide dosing changes
  - Exclude concomitant adrenal insufficiency (morning cortisol level)

- **Continue immunotherapy if asymptomatic**
  - Consider propranolol (10-20 mg every 4-6h 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
  - If persistent thyrotoxicosis, consider evaluation for Graves’ disease

Thyrotoxicosis often evolves to hypothyroidism (50-90%) requiring treatment with thyroid hormone replacement (see Clinical, primary hypothyroidism above for levothyroxine dosing)

---

Footnotes in Later Slide

irAEs, immune-related adverse event; T4, Thyroxine; TSH, thyroid stimulating hormone; T3, Triiodothyronine

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Specific Management of irAEs

Endocrine: Thyroid, Hypophysitis

Assessment

- Evaluate \(^9,7\):
  - Morning cortisol and ACTH
  - LH, FSH, testosterone in men, estrogen in premenopausal women
  - MRI brain +/- contrast with pituitary/sellar cuts, if symptomatic \(^6\)

Management

- Endocrine consultation
  - **Hold immunotherapy until acute symptoms resolve and hormone replacement initiated**
    - If acute, severe symptoms with concern for mass effect, may carefully consider high-dose steroids
    - Treat with hormone placement as indicated \(^u, v, w\)
      - Secondary adrenal insufficiency (low ACTH, low cortisol)
        - Steroid replacement \(^u\)
        - Alert bracelet recommended
        - Patient education for stress dosing with illness, surgery, infection, etc
      - Central hypothyroidism (Low TSH, low FT4)
        - Thyroid hormone replacement \(^v\)
        - Follow free t4 level for thyroid hormone dose titration

Footnotes in Later Slide

ACTH, adrenocorticotropic hormone; DHEA-S, dehydroepiandrosterone sulfate; FSH, follicle-stimulating hormone; irAEs, immune-related adverse event; LH, luteinizing Hormone, MRI, magnetic resonance imaging; T4, thyroxine; TSH, thyroid stimulating hormone

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Specific Management of irAEs

Endocrine: Adrenal

**Assessment**

- Rare diagnosis that is not usually associated with checkpoint immunotherapy
- If concern for this diagnosis, recommend endocrine consultation

**Primary adrenal insufficiency** (high ACTH with low morning cortisol, abnormal cosyntropin stimulation test)
Specific Management of irAEs

Endocrine irAEs

a. Elevated fasting sugars <200 mg/dL should be managed per national/institutional guidelines and/or by a patient's primary care physician (PCP) or endocrinologist.
b. Consider HgA1c measurement.
c. High-dose corticosteroids may induce or exacerbate hyperglycemia. Consider endocrinology referral and appropriate management if symptomatic and/or persistently uncontrolled.
d. Symptoms of diabetic ketoacidosis (DKA) may include excessive thirst, frequent urination, general weakness, vomiting, confusion, abdominal pain, dry skin, dry mouth, increased heart rate, and fruity odor on the breath.
e. In patients who are critically ill/ill-appearing with sugars >200 mg/dL /typically 300-500 mg/dL), urgent/emergent evaluation for DKA is indicated.
f. The development of type I DM is rare but can be life-threatening if insulin therapy is not provided. Once new type I DM is diagnosed, management and monitoring should be directed by endocrinology team. Autoantibodies may not be present.
g. Evaluate for signs/symptoms of pancreatic exocrine insufficiency, and supplement if needed.
h. Insufficient evidence to suggest corticosteroids may reverse type I DM induced by immunotherapy, and may complicate glycemic control.
i. Institutional guidelines may include but are not limited to: IV fluids +/- potassium supplementation, IV insulin, hourly glucose, serum ketones, blood pH, and anion gap.
j. Elevated TSH with normal free T4
k. Generally, elevated TSH (>10) with low free T4, clinical symptoms.
m. For patients without baseline thyroid function abnormalities or who are asymptomatic, can increase thyroid function testing interval to every 12-18 weeks as indicated.
n. Levothyroxine oral daily ~1.6mcg/kg with goal of getting TSH to reference range or age-appropriate range; reduce dose by 10% to avoid hyperthyroidism in patient populations that may be sensitive to thyroid supplementation (eg, elderly populations or patients with comorbidities). For young healthy patients with TSH > 10 with low free T4, a full replacement dose is estimated at 1.6 mcg/kg. This dose can be reduced 10% or more in elderly patients, those with coronary artery disease (CAD) and/or per provider recommendations. Alternatively, in older patients or those with comorbidities, including CAD, starting doses of 50 to 100 mcg can also be considered with follow-up TSH levels at 4-6 weeks and further dose adjustments to achieve TSH in reference range. For subclinical hypothyroidism and/or in elderly or in patients with underlying CA, TSH >10 with normal T4, options for therapy may include the above dosing options; alternatively, as these patients have intact thyroid function, most often empiric supplemental levothyroxine doses of ~50-100 mcg maybe considered rather than weight-based dosing.
Specific Management of irAEs

Endocrine irAEs

Defined as suppressed TSH that may be: a) subclinical if free T4 normal, b) clinical if high free T4. The majority of suppressed TSH (<0.01) are due to transient or progressive 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.

Usual duration for thyrotoxicosis from checkpoint immunotherapy is 4-6 weeks. Graves’ disease evaluation with thyroid-stimulating hormone receptor antibody (TRAb) or thyroid-stimulating immunoglobulin (TSI) measurement or thyroid uptake scan can be considered in patients with persistent thyrotoxicosis.

Hypophysitis may present with symptoms such as headache, dizziness, nausea/emesis, anorexia, and/or severe fatigue. Patients may have low blood pressure, lethargy, or confusion. Lab testing often shows low ACTH, low cortisol, and sometimes low serum sodium or abnormalities of other pituitary hormones. Cosyntropin stimulation testing can be normal in acute secondary adrenal insufficiency and should not exclude hypophysitis. Symptoms may be acute or subacute.

If a patient has polyuria/polydipsia and elevated serum sodium, consider workup for diabetes insipidus; however, this is exceedingly rare with only a few case reports and more often due to tumor metastases.

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.

If severe acute symptoms, such as concern for optic chiasm compression or mass effect, may consider high-dose steroids (prednisone or methylprednisolone 1 mg/kg/day) as indicated until symptoms resolve (1-2 weeks) then rapid taper to physiologic replacement. Some studies suggest increased mortality in patients treated with high-dose steroids for hypophysitis.

Hormone replacement for pituitary damage should include physiologic steroid replacement; or secondary adrenal insufficiency. Generally, initial dosing is hydrocortisone 20 mg PO every AM and 10 mg PO every PM in ambulatory patients. Further titration of the hydrocortisone replacement is best guided by an endocrinologist. Acutely symptomatic or hospitalized patients may require stress dose hydrocortisone (eg, 50 mg every 6-8 h) and endocrinology consultation. Patients may require physiologic replacement hormones indefinitely.

See Clinical (overt) primary hypothyroidism on ICI_ENDO-2 (earlier slide) for levothyroxine dosing.

For central hypogonadism (low LH, low FSH, and low sex hormone, not due to underlying illness) may consider testosterone supplementation in males and estrogen in pre-menopausal women if not otherwise contraindicated.
# Specific Management of irAEs

## Pulmonary

### Presentation

- Pneumonitis is the most common pulmonary irAE and one of the most common causes of ICI-related death
  - May be asymptomatic or characterized by shortness of breath, cough, wheezing, chest pain, fatigue, increased need for supplementary oxygen, reduced tolerance for exercise
- Less common irAEs include pleural effusion, pulmonary sarcoidosis, and sarcoid-like granulomatous reactions

### Incidence

Anti-PD-1/PD-L1 and anti-CTLA-4: <5% (all grade) and 1%–2% (grade≥3)

### Onset

- Timing of pneumonitis varies by tumor type (median onset is ~2 mo in NSCLC and ~5 mo in melanoma)

### Overview

- Preexisting lung diseases complicate the diagnosis of pneumonitis

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CTLA-4, cytotoxic T-lymphocyte–associated protein 4; Grade, grade; ICI, immune checkpoint inhibitor; irAEs, immune-related adverse event.; NSCLC, non-small cell lung cancer; PD-1, programmed cell death 1; PD-L1, programmed death ligand 1.

# Specific Management of irAEs

## Pulmonary: Pneumonitis

### Symptom Grade

<table>
<thead>
<tr>
<th>Mild (G1)</th>
<th>Moderate (G2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Consider holding immunotherapy</strong></td>
<td><strong>Hold immunotherapy</strong></td>
</tr>
<tr>
<td>Reassess in 1-2 weeks</td>
<td>Consider pulmonary consultation</td>
</tr>
<tr>
<td>➢ H&amp;P</td>
<td>Minimally invasive evaluation:</td>
</tr>
<tr>
<td>➢ Pulse oximetry (resting and with ambulation)</td>
<td>➢ Consider infectious workup:</td>
</tr>
<tr>
<td>Consider chest CT with contrast</td>
<td>➢ Nasal swab for potential viral pathogens</td>
</tr>
<tr>
<td>➢ Consider repeat chest CT in 4-6 weeks or as clinically indicated if patient develops symptoms</td>
<td>➢ Sputum culture (including bacterial, fungal, and acid-fast bacilli [AFB]), blood culture, and urine antigen test (pneumococcus, legionella)</td>
</tr>
<tr>
<td></td>
<td>Consider chest CT with contrast and repeat chest CT in 3-4 weeks</td>
</tr>
<tr>
<td>Invasive evaluation</td>
<td>Consider bronchoscopy with bronchoalveolar lavage (BAL) (send for institutional immunocompromised panel) and consider transbronchial lung biopsy if clinically feasible</td>
</tr>
<tr>
<td></td>
<td>Consider empiric broad-spectrum antibiotics (including coverage for atypical pathogens) if infection has not yet been fully excluded</td>
</tr>
<tr>
<td></td>
<td>Prednisone/methylprednisolone 1-2mg/kg/day</td>
</tr>
<tr>
<td></td>
<td>Monitor every 3-7 days with:</td>
</tr>
<tr>
<td>➢ H&amp;P</td>
<td>➢ Pulse oximetry (resting and with ambulation)</td>
</tr>
<tr>
<td></td>
<td>If no improvement after 48-72 hours of corticosteroids, treat as grade 3</td>
</tr>
</tbody>
</table>

**Footnotes in Later Slide**

CT, computed tomography; H&P, History and physical; irAEs, immune-related adverse event

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Specific Management of irAEs

**Pulmonary: Pneumonitis**

<table>
<thead>
<tr>
<th>Symptom Grade</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe (G3-4)</td>
<td></td>
</tr>
</tbody>
</table>

### Permanently discontinue immunotherapy
- Inpatient care
- Pulmonary and infectious disease consultation
- Minimally invasive evaluation
  - Infectious workup:
    - Consider that patient may be immunocompromised
    - Nasal swab for potential viral pathogens
    - 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) 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
- Methylprednisolone 1-2mg/kg/day. Assess response within 48 hours and plan taper of ≥ 6 weeks
- Consider adding any of the following if no improvement after 48 hours:
  - Infliximab® 5 mg/kg IV, a second dose may be repeated 14 days later at the discretion of the treating provider
  - IVIG
  - Mycophenolate mofetil 1-1.5g BID then taper in consultation with pulmonary service.

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AFB, acid-fast bacilli; BAL, bronchoalveolar lavage; irAEs, immune-related adverse event; IVIG, Intravenous immunoglobulin

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Specific Management of irAEs

Pulmonary: Pneumonitis

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 G3-severe symptoms involve lung lobes or >50% of lung parenchyma, limiting self-care ADLS, oxygen indicated; G4-life-threatening respiratory compromise.
g CT with contrast to rule out other etiologies if not contraindicated.
h Viral pathogen assessment should include COVID-19.
i Immunocompromised panel should include bacterial culture and gram stain; AFB culture and stain; fungal immunoassay, culture, and silver stain; CMV, HSV, PJP, and respiratory virus PCR.
j Treat until symptoms improve to Grade≤ 1 then taper over 4-6 weeks.
k If clinically indicated and appropriate, monitoring can be done with telemedicine.
l Options are listed in alphabetical order. There are no data to support the use of one over another.
m An FDA-approved biosimilar is an appropriate substitute for infliximab.
n Total dosing should be 2 g/kg, administered in daily divided doses over 2 to 5 days or as per package insert.
Specific Management of irAEs

Renal

- Renal irAEs are uncommon and are typically asymptomatic, but some data suggest these irAEs are underreported
  - Some studies have reported low-grade kidney injury in 25%–29% of patients
  - Most patients with acute kidney injury present with acute interstitial nephritis
    - Symptoms may include oliguria, hematuria, peripheral edema, and anorexia

<table>
<thead>
<tr>
<th>Presentation¹</th>
<th>Anti-PD-1/PD-L1/anti-CTLA-4: 1-2% ICPIs combinations. 4.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence²</td>
<td>Anti-PD-1/PD-L1/anti-CTLA-4: 1-2% ICPIs combinations. 4.5%</td>
</tr>
<tr>
<td>Onset¹</td>
<td>With anti–PD-1: 3–10 months after initiation</td>
</tr>
<tr>
<td></td>
<td>With anti–CTLA-4: 2–3 months after initiation</td>
</tr>
</tbody>
</table>

CTLA-4, cytotoxic T-lymphocyte–associated protein 4; Grade, grade; irAEs, immune-related adverse event; PD-1, programmed cell death 1; PD-L1, programmed death ligand 1.

Specific Management of irAEs
Renal: Elevated serum creatinine/acute kidney injury

### Assessment/Grading

- Limit/discontinue nephrotoxic medications and dose adjust to creatinine clearance
- Evaluate potential alternative etiologies (recent IV contrast, medications, fluid status, UTI)<sup>b</sup>
- Spot urine protein/creatinine ratio<sup>c</sup>

### Symptom Grade

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (G1)</td>
<td>Creatinine 1.5-2x above baseline; increase of ≥0.3 mg/dL</td>
<td>Consider holding immunotherapy&lt;br&gt;Follow urine protein/creatinine ratio every 3-7 days&lt;br&gt;Consider nephrology consult if creatinine remains unchanged over 2 weeks</td>
</tr>
<tr>
<td>Moderate (G2)</td>
<td>Creatinine 2-3x above baseline</td>
<td>Hold immunotherapy&lt;br&gt;Follow urine protein/creatinine ratio every 3-7 days&lt;br&gt;Nephrology consultation&lt;br&gt;Consider renal biopsy if feasible prior to starting steroids&lt;br&gt;Start prednisone 0.5-1 mg/kg/day if other causes are ruled out&lt;sup&gt;f&lt;/sup&gt;&lt;br&gt;For persistent G2 beyond 1 week, prednisone/methylprednisolone 1-2 mg/kg/day&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Severe (G3) or Life-threatening (G4)</td>
<td>Creatinine &gt;3x baseline or &gt;4.0 mg/dL; dialysis indicated</td>
<td>Hold immunotherapy&lt;br&gt;Consider inpatient care&lt;br&gt;Follow urine protein/creatinine ratio every 3-7 days&lt;br&gt;Nephrology consultation&lt;br&gt;Consider renal biopsy if feasible prior to starting steroids&lt;br&gt;Prednisone/methylprednisolone 1-2 mg/kg/day&lt;sup&gt;f&lt;/sup&gt;&lt;br&gt;Consider adding one of the following if kidney injury remains &gt;G2 after 4-6 weeks of steroids (in alphabetical order):&lt;br&gt;  ➢ Azathioprine&lt;br&gt;  ➢ Cyclophosphamide (monthly)&lt;br&gt;  ➢ Cyclosporine&lt;br&gt;  ➢ Infliximab&lt;sup&gt;e&lt;/sup&gt;&lt;br&gt;  ➢ Mycophenolate</td>
</tr>
</tbody>
</table>

### Footnotes in Next Slide

G, grade; immune-related adverse event; irAEs, immune-related adverse event; UTI, Urinary tract infection

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Specific Management of irAEs

Renal: Elevated serum creatinine/acute renal failure

a Azotemia, creatinine elevation, inability to maintain acid/base or electrolyte balance, and urine output change.
b General medical review and testing as warranted for prerenal and postrenal causes. Include medication review for nephrotoxic agents such as NSAIDs and PPIs, and consider obstruction, cardiomyopathy/heart failure, pulmonary hypertension, diuretics, hypovolemia due to primary GI cause, stones, and infection.
c For proteinuria >3 g/24-hour and/or gross or microscopic hematuria check ANA, RF, ANCA, anti-ds-DNA, and serum C3, C4, CH50, hepatitis B and C reflexive panels, SPEP, and UPEP. Consider 24-hour urine collection.
f Treat until symptoms improve to Grade ≤1 then taper over 4-6 weeks.
g An FDA-approved biosimilar is an appropriate substitute for infliximab.
# Specific Management of irAEs

## Cardiovascular Adverse Events (Myocarditis, pericarditis, arrhythmias, impaired ventricular function, conduction abnormalities)

### Presentation
- Cardiovascular irAEs are rare, but can be rapidly fatal
- Myocarditis is an important cardiovascular irAE, but others include:
  - Pericarditis, arrhythmias, impaired ventricular function with heart failure, vasculitis, and venous thromboembolism
- Symptoms include fatigue and weakness with or without more typical cardiac symptoms (arrhythmia, palpitations, chest pain, or signs and symptoms of heart failure)
  - Cardiogenic shock or sudden death may occur in severe cases

### Incidence
- < 0.1% of patients receiving checkpoint inhibitors
  - Combination therapy has greater rates vs monotherapy (CTLA-4 and PD-1 inhibitor combination: 0.28% vs PD-1 monotherapy: 0.06%)

### Onset
- Median onset is 10 weeks after start of therapy (can range widely)

### Overview
- Myocarditis is rare, but has a high fatality rate relative to other irAEs
- Maintain low threshold for suspicion of potential irAE and referral to specialist

---

Specific Management of irAEs
Cardiovascular Adverse Events (Suspected Myocarditis/pericarditis)

**Symptoms/Signs**
- Ventricular arrhythmias/tachycardia
- Heart failure
- Cardiogenic shock
- Conduction abnormalities
- Myositis/myasthenia gravis
- Pericardial effusion
- Differential
  - Myocardial infarction/acute coronary syndrome
  - Vasculitis
  - COVID-19

**Assessment/Grading**
- Immediate cardiology consultation (preferably cardio-oncology)
- ECG (at baseline and with any suspected CV adverse event)
- Telemetry monitoring (inpatient)/topical patch monitor (outpatient)
- Echocardiogram
- Cardiac Biomarkers (troponin I or T, creatine kinase, BNP or NTproBNP; lipid panel)
- Inflammatory biomarkers
  - Consider ESR, CRP, or other inflammatory biomarkers
- Cardiac MRI (if possible)
- Consider cardiac catheterization and/or myocardial biopsy in a specialized center if myocarditis is suspected
- Consider viral titers (especially COVID-19)

**Management**
- Permanently discontinue immunotherapy
- Management is tailored to acuity and response of presentation
- High-dose steroids such as methylprednisolone pulse dosing 1g/day for 3-5 days
  - Switch to oral prednisone, then taper slowly over 4-6 weeks based on clinical response and improvement of biomarkers
- If no improvement within 24 hours on steroids, consider adding other potent immunosuppressive agents:
  - Abatacept
  - Mycophenolate
  - Intravenous immunoglobulin (IVIG)
  - Alemtuzumab
  - Infliximab (Use with extreme caution in patients with reduced LVEF)
  - Anti-thymocyte globulin (ATG)
- ICU-level monitoring
- Temporary or permanent pacing as required

Footnotes in Next Slide
CRP, C-reactive protein; ECG, electrocardiogram; ESR, Erythrocyte Sedimentation Rate; ICU, intensive care unit; IVIG, Intravenous immunoglobulin; MRI, Magnetic resonance imaging; ULN, upper limit of normal; WBC, White blood cells

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Specific Management of irAEs
Cardiovascular Adverse Events (Suspected Myocarditis/pericarditis)

Symptoms/Signs
- Ventricular arrhythmias/tachycardia
- Heart failure
- Cardiogenic shock
- Conduction abnormalities
- Myositis/myasthenia gravis
- Pericardial effusion
- Differential
  - Myocardial infarction/acute coronary syndrome
  - Vasculitis
  - COVID-19

Assessment/Grading
- Immediate cardiology consultation (preferably cardio-oncology)
- ECG (at baseline and with any suspected CV adverse event)
- Telemetry monitoring (inpatient)/topical patch monitor (outpatient)
- Echocardiogram
- Cardiac Biomarkers (troponin I or T, creatine kinase, BNP or NTproBNP, lipid panel)
- Inflammatory biomarkers
  - Consider ESR, CRP, or other inflammatory biomarkers
- Cardiac MRI (if possible)
- Consider cardiac catheterization and/or myocardial biopsy in a specialized center if myocarditis is suspected
- Consider viral titers (especially COVID-19)

Management
- Manage as per usual recommendations
- Consider myocarditis as a contributor

Pericarditis/pericardial effusion

Footnotes in Next Slide
CRP, C-reactive protein; ECG, electrocardiogram; ESR, Erythrocyte Sedimentation Rate; ICU, intensive care unit; IVIG, Intravenous immunoglobulin; MRI, Magnetic resonance imaging; ULN, upper limit of normal; WBC, White blood cells

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Specific Management of irAEs

Cardiovascular Adverse Events (Myocarditis\textsuperscript{a}, pericarditis, arrhythmias, impaired ventricular function, conduction abnormalities)

a Myocarditis symptoms are nonspecific. It is rare, but potentially severe, not viral in etiology, associated with myositis/myasthenia gravis, and is more common with combination therapy. In fatal cases, conduction abnormality were mode 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 CV risk, also consider troponin and NTproBNP at baseline for identifying those at increased risk.
e No evidence specific to immunotherapy-related myocarditis; recommendations drawn from other causes of myocarditis.
h mycophenolate mofetil treatment (0.5–1g every 12 hours).
i Total dosing should be 2g/kg, administered in divided doses per package insert.
j An FDA-approved biosimilar is an appropriate substitute for infliximab.
### Specific Management of irAEs

**Musculoskeletal (Inflammatory Arthritis, Polymyalgia-Like Syndrome, and Myositis)**

| Presentation¹ | • Inflammatory arthritis is a common musculoskeletal/rheumatologic irAE  
| | – Presentation varies and large and/or small joints may be affected  
| | • Other irAEs include polymyalgia-like syndrome, myositis, vasculitis, lupus-like syndromes |
| Incidence¹ | • Arthralgias reported in ~15% of patients (most are low grade)  
| | • Incidence of inflammatory arthritis has not been systematically reported |
| Onset² | • Can occur at any time during treatment; may occur many months after treatment begins |
| Overview² | • Musculoskeletal/rheumatologic irAEs such as inflammatory arthritis tend to be low grade, but severe toxicities that affect QoL and ADL can occur |

ADL, activities of daily living; irAE, immune-related adverse events; QoL, quality of life;
## Specific Management of irAEs
### Musculoskeletal: Inflammatory Arthritis

<table>
<thead>
<tr>
<th>Assessment/Grading</th>
<th>Symptom Grade</th>
<th>Management</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Consider rheumatology consultation</td>
<td>Mild&lt;sup&gt;b&lt;/sup&gt;</td>
<td>• Continue immunotherapy</td>
<td>• Monitor with serial rheumatologic examinations +/- ESR, CRP every 4-6 weeks after treatment&lt;sup&gt;m&lt;/sup&gt;</td>
</tr>
<tr>
<td>• Number of joints involved</td>
<td></td>
<td>• NSAIDS&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>• Functional assessment</td>
<td></td>
<td>• If NSAIDS ineffective, consider low-dose prednisone 10-20 mg daily x 2-4 weeks; if not improving, treat as moderate</td>
<td></td>
</tr>
<tr>
<td>• X-ray, joint ultrasound, or joint MRI</td>
<td></td>
<td>• Consider intra-articular steroids in affected joint(s), depending on joint location and number involved</td>
<td></td>
</tr>
<tr>
<td>• Anti-nuclear antibodies (ANA), anticyclic citrullinated peptide (anti-CCP), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF)</td>
<td>Moderate</td>
<td>• Continue holding immunotherapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Prednisone 0.5 mg/kg/day x 2-3 weeks, if treat as severe if no improvement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe&lt;sup&gt;c&lt;/sup&gt;</td>
<td>• Hold or permanently discontinue&lt;sup&gt;d&lt;/sup&gt; immunotherapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Prednisone/methylprednisolone 1 mg/kg/day&lt;sup&gt;e&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td>• If no improvement by week 1 or if unable to taper steroids by week 2, rheumatology consultation for consideration of additional disease modifying anti-rheumatic drugs depending on clinical phenotype of inflammatory arthritis. Options include infliximab, methotrexate, tocilizumab, sulfasalazine, azathioprine, adalimumab, etanercept, hydroxychloroquine</td>
<td></td>
</tr>
</tbody>
</table>

**Footnotes in Next Slide**

ADL, activities of daily living; CRP, C-reactive protein; ESR, Erythrocyte Sedimentation Rate; IVIG, Intravenous immunoglobulin; irAE, immune-related adverse events; MRI, Magnetic resonance imaging;

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Specific Management of irAEs

Musculoskeletal (Inflammatory Arthritis, Polymyalgia-Like Syndrome, and Myositis)

a Clinical symptoms: joint pain, joint swelling; inflammatory symptoms: stiffness after inactivity, improvement with heat.
b Mild in severity or only 1 joint involved.
c Limits ADLs, presence of joint erosions.
e Consider other non-opioid medications, eg, COX2 inhibitors or gabapentin/pregabalin.
g Treat until symptoms improve to grade \(< 1\), then taper over 4-6 weeks.
i 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.
j An FDA-approved biosimilar is an appropriate substitute for infliximab.
k An FDA-approved biosimilar is an appropriate substitute for adalimumab.
l An FDA-approved biosimilar is an appropriate substitute for etanercept.
m Consider ESR, CRP to monitor response if elevated at the onset of therapy.
Specific Management of irAEs

Fatigue

<table>
<thead>
<tr>
<th>Assessment/Grading&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Symptom Grade&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Management&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical exam including vital signs (weight, temperature, heart rate, RR, BP, O₂ saturation (rest and walking))</td>
<td>Mild (G1) (Relieved by rest)</td>
<td>Continue immunotherapy</td>
<td>Call for new or worsening symptoms</td>
</tr>
<tr>
<td>Labs</td>
<td>Moderate (G2) (Not relieved by rest; limiting ADLs)</td>
<td>Continue immunotherapy if impact on ADLs can be mitigated with active management</td>
<td>Address any abnormalities for vital signs or labs</td>
</tr>
<tr>
<td>CBC</td>
<td>Severe (G3-4) (Not relieved by rest, limiting self care)</td>
<td>Hold or consider discontinuing immunotherapy</td>
<td>Consider follow-up in 5-7 days (by phone or visit)</td>
</tr>
<tr>
<td>CMP</td>
<td></td>
<td>Consultation or treatment based on abnormalities</td>
<td>Call for new or worsening symptoms</td>
</tr>
<tr>
<td>TSH, free T4 (if not recently done)</td>
<td></td>
<td>If no treatable cause found, may consider a trial of low-dose steroids</td>
<td>Address any abnormalities for vital signs or labs</td>
</tr>
<tr>
<td>Morning cortisol</td>
<td></td>
<td></td>
<td>Consider disease progression, other medical condition, or other irAE</td>
</tr>
<tr>
<td>Morning ACTH (if morning cortisol is subnormal)</td>
<td></td>
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<tr>
<td>Morning testosterone (male patients)</td>
<td></td>
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<tr>
<td>Medication review</td>
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</tbody>
</table>

Footnotes in Next Slide

ACTH, Adrenocorticotropic hormone; BP, blood pressure; CBC, complete blood count; CMP, comprehensive metabolic panel; G, grade; O₂, oxygen; RR, respiration rate; TSH, thyroid stimulating hormone; T4, thyroxine

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Specific Management of irAEs

Fatigue

If diagnostic studies indicate central hypothyroidism and/or central/secondary adrenal insufficiency, see respective slides for treatment recommendations.

Based on physical signs and labs, management may include hydration, medication adjustment, education, diet, and sleep hygiene. If symptoms are unrelated to immunotherapy, see NCCN Guidelines for Cancer-Related Fatigue.
## Specific Management of irAEs

### Summary

Guidelines on specific management of ICPIs irAEs and patient monitoring during and after ICPIs treatment available from main clinical societies: ASCO, NCCN, SITC, ESMO

<table>
<thead>
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<th>GUIDELINES for MANAGEMENT of ICPIs-associated irAES</th>
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