Practical Management of Immunotherapy-Related Toxicity

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What is an Immune Related Event?

- AEs
- Drug-related AEs
- irAEs

How many events are Immune Related??
Treatment ??
Monitor ??
Outcome ??
**GASTROINTESTINAL adverse events**, such as, e.g.:
- Diarrhea
- Abdominal pain
- Blood in the stool
- Bowel perforation
- Peritoneal signs

**HEPATIC adverse events/CHANGES IN LABORATORY VALUES**, such as, e.g.:
- Abnormal liver function tests (e.g. AST, ALT or total bilirubin)

**DERMATOLOGICAL adverse events**, such as, e.g.:
- Pruritus
- Rash

**NEUROLOGICAL adverse events**, such as, e.g.:
- Unilateral or bilateral muscle weakness
- Sensory alterations
- Paresthesia

**ENDOCRINE ADVERSE EVENTS**, such as, e.g.:
- Tiredness
- Headache
- Changes in mental health
- Abdominal pain
- Unusual bowel habits
- Hypotension

**OTHER IMMUNE-RELATED ADVERSE EVENTS**
- Uveitis, iritis or conjunctivitis
- Elevated amylase and/or lipase levels
- Eosinophilia, hemolytic anemia
- Glomerulonephritis, pneumonitis
- Multiorgan failure
- Thyroiditis
- Sarcoidosis
Pathophysiology of ICI-mediated irAE

• 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 cell, autoantibodies, and/or proinflammatory cytokines (eg, interleukin-17)
  - T cell activity directed at antigens presents in both tumor cell and healthy tissue
  - Inflammation in normal tissues could result from elevated level of inflammatory cytokines as a downstream effect of T-cell activation
  - Direct binding of immune checkpoint antibodies to targets expression normal tissue (eg, CTLA expression in pituitary) could lead to complement-mediated inflammation
  - Immunotherapy might increase the levels of preexisting autoreactive antibodies.

Immune related adverse events associated with ICI, *NEJM* 2018; 378: 158-168
NCCN guideline Version 1, 2019
Early and later onset irAE may result from distinct mechanisms

**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**, less common, can include neurologic events and hypophysitis.
- These irAEs tend to be more localized, organ specific reactions.

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Immune related adverse events associated with ICI, *NEJM* 2018; 378: 158-168
NCCN guideline Version 1, 2019
General aspects of irAEs

• Toxicities from immune checkpoint inhibitors (ICI) can be divided into
  - Infusion reactions and immune-related adverse events (irAEs)
  - Adverse events of special interest (AEOsI)

• irAEs occur quite early, mostly within *weeks to 3 months* after initiation of ICI
• The role of tissue biopsy in the diagnosis of irAEs is not established.
• Some recommendations suggest tissue biopsy in higher grade (3 and 4) toxicity where there is diagnostic doubt about the aetiology of the complication and management would be altered by the outcome of the biopsy procedure

Distribution of (A) grade 1 - 2 and (B) grade 3 - 5 irAEs for all tumor types in the main clinical trials with ICIs as single therapies

Brahmer et al. JCO 2018
Adverse events of special interest noted with ICIs

Comprehensive Meta-analysis of Key Immune-Related Adverse Events from CTLA-4 and PD-1/PD-L1 Inhibitors in Cancer Patients

Table 2. Incidence of all-grade and high-grade of immune-related toxicities of novel ICIs in cancer patients

<table>
<thead>
<tr>
<th>Immune-related toxicities</th>
<th>No. trials</th>
<th>No. events</th>
<th>Incidence, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colitis</td>
<td>16</td>
<td>206/5,442</td>
<td>2.3 (1.3–3.9)</td>
</tr>
<tr>
<td>AST</td>
<td>14</td>
<td>330/3,855</td>
<td>6.5 (3.3–12.4)</td>
</tr>
<tr>
<td>Rash</td>
<td>19</td>
<td>952/5,777</td>
<td>13.9 (10.6–18.0)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>15</td>
<td>244/4,622</td>
<td>5.1 (3.8–6.8)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>15</td>
<td>119/4,599</td>
<td>2.6 (2.0–3.7)</td>
</tr>
<tr>
<td>High grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colitis</td>
<td>16</td>
<td>119/5,442</td>
<td>1.5 (0.9–2.5)</td>
</tr>
<tr>
<td>AST</td>
<td>14</td>
<td>94/3,855</td>
<td>1.5 (0.7–3.4)</td>
</tr>
<tr>
<td>Rash</td>
<td>18</td>
<td>50/5,299</td>
<td>1.1 (0.7–1.7)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>14</td>
<td>5/4,144</td>
<td>0.3 (0.2–0.5)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>15</td>
<td>42/4,599</td>
<td>1.1 (0.7–1.7)</td>
</tr>
</tbody>
</table>

Table 4. Comparison between PD-1/PD-L1 and CTLA-4 inhibitors

<table>
<thead>
<tr>
<th>Immune-related toxicities</th>
<th>PD-1/PD-L1 inhibitors RR (95% CI)</th>
<th>CTLA-4 inhibitors RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colitis</td>
<td>3.36 (1.36–8.33)</td>
<td>11.3 (6.05–21.1)</td>
<td>0.054</td>
</tr>
<tr>
<td>AST</td>
<td>1.71 (1.01–2.89)</td>
<td>1.92 (0.94–3.93)</td>
<td>0.745</td>
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<tr>
<td>Rash</td>
<td>1.59 (0.90–2.82)</td>
<td>3.94 (3.02–5.14)</td>
<td>0.006</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>8.05 (4.26–15.2)</td>
<td>4.64 (1.42–15.2)</td>
<td>0.352</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>3.8 (1.23–12.1)</td>
<td>11.1 (0.62–199.8)</td>
<td>0.562</td>
</tr>
<tr>
<td>High grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colitis</td>
<td>2.47 (0.90–6.72)</td>
<td>22.5 (6.37–79.4)</td>
<td>0.021</td>
</tr>
<tr>
<td>AST</td>
<td>1.26 (0.38–4.16)</td>
<td>5.06 (1.26–20.3)</td>
<td>0.168</td>
</tr>
<tr>
<td>Rash</td>
<td>0.91 (0.40–2.10)</td>
<td>3.55 (1.37–9.19)</td>
<td>0.052</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>0.85 (0.25–2.84)</td>
<td>2.02 (0.39–10.5)</td>
<td>0.421</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>1.49 (0.80–2.79)</td>
<td>3.02 (0.12–74.0)</td>
<td>0.798</td>
</tr>
</tbody>
</table>

- Incidence of all-grade irAEs - **58%** with anti CTLA-41 & **35%** with anti PD-1
- Majority of irAEs: grade 1-2 (most frequently in skin or GI tract)
- Grade 3-5 events: <5% of patients in monotherapy with anti PD-1/PD-L1
Onset of irAEs

irAEs occur at any time during treatment\(^1\)
- From the first few weeks or months to up to a year after treatment initiation\(^2,3\)
- Most irAEs will occur in the first few doses\(^4\)
- The pattern of onset vary by organ system\(^4\)

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Median Time to onset and median duration treatment-related select AEs:

- Median time to onset and median duration of immune-mediated adverse reactions are presented based on 2799 patients with NSCLC and melanoma treated with pembrolizumab.

### Median Time to Onset

- **Pneumonitis**: 3.3 (2 days–19.3 mo)
- **Colitis**: 3.5 (10 days–16.2 mo)
- **Hepatitis**: 1.3 (8 days–21.4 mo)
- **Hypophysitis**: 3.7 (1 day–11.9 mo)
- **Hyperthyroidism**: 1.4 (1 day–21.9 mo)
- **Hypothyroidism**: 3.5 (1 day–18.9 mo)
- **Nephritis**: 5.1 (12 days–12.8 mo)

### Median Duration

- **Pneumonitis**: 1.5 (1 day–17.2+ mo)
- **Colitis**: 1.3 (1 day–8.7+ mo)
- **Hepatitis**: 1.8 (8 days–20.9+ mo)
- **Hypophysitis**: 4.7 (8+ days–12.7+ mo)
- **Hyperthyroidism**: 2.1 (3 days–15.0+ mo)
- **Hypothyroidism**: NR (2 days–27.7+ mo)
- **Nephritis**: 3.3 (12 days–8.9+ mo)

*mo = months, NR = not reached, NSCLC = non-small cell lung cancer.

1. KYTRUDA Thailand Prescribing Information
Management of ICI-Related Toxicity

• The primary facets of irAEs management include:
  1. Recognition
  2. Grading of toxicity
  3. Immunosuppression
  4. Individualized modification to ICI administration

• Early recognition of symptoms and prompt intervention are key goals for management of immunotherapy-related toxicity
Management of ICI-Related Toxicity

Mild to moderate AEs
- Symptomatic management
- Delay in ICI may be required until AE resolve to grade 1
- Corticosteroids may be required if AE does not improve
- If hormone replacement is required, it is usually for lifetime

Severe AEs
- Discontinue ICI
- Initiate steroid immediately
- Additional immunosuppressant therapy may be required for steroid refractory
- Inpatient care and supportive treatment
Mild transient reaction

Infusion-related reaction from ICIs

- Severe reaction occurred in < 1% of patients across all other ICIs.
- Atezolizumab 1.3%, durvalumab 2.2%, <10% for PD-1 inhibitor and Ipi <1%
- Most common with avelumab (all grade -25%, grade ¾ - 0.7%), majority occur during first infusion. Paracetamol and diphenhydramine are recommend prior to infusion during the first 4 cycles.

\[\text{Infusion-related reactions}^{a} \xrightarrow{\text{Mild transient reaction}} \text{Mild (G1)}^{b} \text{OR Moderate (G2)}^{c} \xrightarrow{\text{Severe (G3–4)}^{d}} \text{• Treat per institutional guidelines} \]

- Physical exam
- Vital signs
- Pulse oximetry
- ECG (if chest pain or sustained tachycardia)

- Treat per institutional guidelines
- Consider hold or slow the rate of infusion
- Continue immunotherapy
- Consider premedication with acetaminophen and diphenhydramine with future infusions
- Permanently discontinue immunotherapy
- There are no data to guide the use of alternate immune checkpoint inhibitors
Immune-related skin toxicity

• Ipilimumab in 43%–45% or PD-1 in 34% (nivo and pembro)
• Usually develop early in the course of treatment (within the first few)
• Serious skin AEs are rare and do not usually require dose reductions or treatment discontinuation
• The most frequent skin AEs are rash (maculopapular and pustulopapular), pruritus and vitiligo
• More rarely, other skin AEs have been reported: alopecia areata, stomatitis, xerosis, cutis, photosensitivity, toxic epidermal necrolysis, Steven-Johnson syndrome and DRESS
• Grade 1 (<10% BSA) Grade 2 (10-30% BSA) - continue ICI. topical emollients, antihistamines, topical corticosteroid
  Prednisolone 0.5-1 mg/kg/day (Gr2)
• Grade 3 (>30% BSA), interrupt ICI and topical emollients, antihistamines and high strength corticosteroid creams
  Prednisolone 0.5-1 mg/kg/day
• Grade 4, discontinue ICI (permanently), consider admitting patient and Start i.v. corticosteroids [1–2mg/kg (methyl)prednisone] and taper based on response of AE.

• Thyroid dysfunction is most common upon treatment with ICI
• Both hyper- and hypothyroidism have been reported, although hypothyroid disorders are more common
• Ipilimumab: 1% - 5%, and anti-PD-1/PD-L1 : 5% - 10%
• Pathogenesis of thyroid disorders following IO – unclear
• It is thought to be mediated by T cells and not by B cell autoimmunity
• In most cases, thyroid dysfunction is found by routine blood tests they should be carried out before every infusion or at least once a month (in the case of 2-weekly infusions)
ICPi monitoring and management: thyroid function

Baseline Endocrine Panel:
- TSH, FT4, T3* TFTs

Baseline abnormal values do not preclude treatment; discuss with endocrinologist if uncertain when indicated.

Monitoring during treatment:
- Anti-CTLA4 (including combination with anti-PD-1)
  - TFTs every cycle
  - TFTs 4-6 weeks after cycle 4 (i.e., with restaging CT)

Late endocrine dysfunction can occur
- Anti-PD-1/Anti-PD-L1
  - TFTs every cycle for first 3 months, every second cycle thereafter (in case of 2-weekly schedule)
  - Cortisol as indicated by symptoms/falling TSH

A falling TSH across two measurements with normal or lowered T4 may also suggest pituitary dysfunction and weekly cortisol measurements should be performed (see also Figure 6).

If TSH is abnormal, refer to algorithm below. Iodine from CT scans may impact TFTs.

Hypothyroidism: Low FT4 with elevated TSH or TSH > 10 with normal FT4
- Treatment: Thyroxine 0.5-1.5 μg/kg (start low in elderly, if cardiac history)
- Continue ICPI

Thyrotoxicosis (DDx thyroiditis, Grave’s disease):
- Investigations: Anti-TSH Receptor Ab, anti-TPO Ab, nuclear medicine thyroid uptake scan
- Treatment: Propranolol or atenolol for symptoms; consider carbimazole if anti-TSH Receptor Ab positive
- Painful thyroiditis – consider prednisolone 0.5 mg/kg and taper
- If unwell, withhold ICPI and consider restarting when symptoms controlled.
### Management of Immune Checkpoint Inhibitor-Related Toxocities

#### Endocrine Adverse Event(s)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Assessment</th>
<th>Management</th>
</tr>
</thead>
</table>
| Asymptomatic/subclinical hypothyroidism *\(^b\)* | Monitor thyroid-stimulating hormone (TSH), free T4 every 4–6 weeks *\(^k\)*  
  - If TSH elevated, proceed based on TSH levels as follows or repeat TSH, free T4 in 4–6 weeks  
  + Elevated TSH (>10)  
  + Normal free T4  
  + Low free T4  
  | Continue immunotherapy  
  - Consider levothyroxine *\(^l\)*  
  |  
| Clinical, primary hypothyroidism *\(^i\)* | Monitor TSH, free T4 every 4–6 weeks *\(^k\)*  
  | Continue immunotherapy  
  - Consider endocrine consultation  
  - Thyroid hormone supplementation *\(^l\)*  
  - Exclude concomitant adrenal insufficiency (AM cortisol level)  
| Thyrotoxicosis *\(^l\)* | Low or suppressed TSH with high free T4/total T3, consider thyroid peroxidase (TPO) antibody and thyroid-stimulating hormone receptor antibody (TRAb)  
  - Consider endocrine consultation if symptomatic  
  | Continue immunotherapy if asymptomatic  
  - Consider propranolol (10–20 mg every 4–6 h as needed) or atenolol or metoprolol as needed for symptoms until thyrotoxicosis resolves  
  |  

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

**Hypophysitis/ Adrenalitis - unexplained fatigue**
- Hypophysitis - More frequent with CTLA4
- Brain MRI - a swollen or enlarged pituitary gland may be visible
- *Low TSH, ACTH and FSH/LH* point towards hypophysitis as the most likely diagnosis
- High dose corticosteroids if headache of visual deficits from hypophysitis
- Adrenal Insufficiency: replacement corticosteroid, can resume ICI (stress steroids as needed)

**Diabetes mellitus/ Diabetic ketoacidosis (DKA)- Endocrine Consult**
- DM - more common with PD-1 and PD-L1 blockade, this could be either type 1 or type 2DM.
- C-peptide and Abs against glutamic acid decarboxylase (GAD) and islet cell should be measured to distinguish between type 1 and type 2DM.
- Insulin (can be difficult to control initially)
Immune-related endocrinopathies

Symptomatic endocrinopathy
- Evaluate endocrine function
- Consider pituitary scan

Symptomatic with abnormal lab/pituitary scan:
- Delay I-O therapy per protocol
- 1-2 mg/kg/day methylprednisolone IV or PO equivalent
- Initiate appropriate hormone therapy

No abnormal lab/pituitary MRI scan but symptoms persist:
- Repeat labs in 1-3 weeks / MRI in 1 month

If improves (with or without hormone replacement):
- Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections
- Resume I-O therapy per protocol
- Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component

Suspicion of adrenal crisis (e.g. severe dehydration, hypotension, shock out of proportion to current illness)
- Delay or discontinue I-O therapy per protocol
- Rule out sepsis
- Stress dose of IV steroids with mineralocorticoid activity
- IV fluids
- Consult endocrinologist
- If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
ICI cause pulmonary irAE by:
- Affecting tissue infiltrating lymphocytes
- Changing cytokine profiles
- Modulating immune checkpoints associated with pulmonary autoimmune diseases
Immune-related pneumonitis

• The incidence: more frequent in anti-PD-1 than anti CTLA4
• The combination of anti-PD-1/PD-L1 with CTLA4 - increases risk up to 3 times compared with monotherapy
• Occur at any time, pneumonitis tends to occur later than other irAEs, commonly some months after treatment was initiated
• Radiological features are not pathognomonic, ground glass opacities, a cryptogenic organizing pneumonia-like appearance and interstitial pneumonia pattern
• Lung biopsy is not required for subsequent patient management
• Immunosuppressive should be started immediately in suspicious cases
• Ideally, an infection should be ruled out by bronchoscopy, especially in the case of grade > 2 pneumonitis
Immune-related pneumonitis

Figure 3: Different Radiographic Patterns of Checkpoint Blockade–Associated Pneumonitis Seen on CT Scanning in a Single Patient Treated With Ipilimumab and Nivolumab—Pneumonitis secondary to ipilimumab is shown in the left-hand panel, and pneumonitis secondary to nivolumab is shown in the center and right-hand panels. Red arrows indicate areas of radiologic abnormality.
One lobe, or <25% of lung parenchyma

Pneumonitis

Mild (G1)

Moderate (G2)

Severe (G3–4)

See ICI_PULM-2

**PULMONARY ADVERSE EVENT(S)**

**GRADING**

- Mild (G1): One lobe, or <25% of lung parenchyma
- Moderate (G2)
- Severe (G3–4)

**MANAGEMENT**

- Consider holding immunotherapy†
- Reassess in 1–2 weeks
  - H&P
  - Pulse oximetry (resting and with ambulation)
  - Consider chest CT with contrast§
  - Consider repeat chest CT in 4 weeks or as clinically indicated for worsening symptoms

- Hold immunotherapy†
- Pulmonary consultation
- Consider infectious workup:
  - Nasal swab for potential viral pathogens
  - Sputum culture, blood culture, and urine culture
- Consider bronchoscopy with bronchoalveolar lavage (BAL) to rule out infection and malignant lung infiltration
- Consider chest CT with contrast§
  - Repeat chest CT in 3–4 weeks
- Recommend infectious evaluation with institutional immunocompromised panel
- Consider empiric antibiotics if infection has not yet been fully excluded
- Prednisone/methylprednisolone 1–2 mg/kg/day³
- Monitor every 3–7 days with:
  - H&P
  - Pulse oximetry (resting and with ambulation)
  - If no improvement after 48–72 hours of corticosteroids, treat as grade 3

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† Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging as ground-glass opacities).

‡ Asymptomatic, confined to one lobe of the lung or <25% of lung parenchyma; clinical or diagnostic observations only.

§ G3–severe symptoms involve all lung lobes or >50% of lung parenchyma; clinical or diagnostic observations only.

See Principles of Immunosuppression (IMMUNOC-A).

See Principles of Immunosuppression Rechallenge (IMMUNOC-G).

CT with contrast to rule out other etiologies if not contraindicated.

³ Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
G3 - Symptoms involve all lobes or >50% of parenchyma

**Severe (G3–4)**

- **Pneumonitis**

### Management

- Permanently discontinue immunotherapy
- Inpatient care
- Infectious workup:
  - Consider that patient may be immunocompromised
  - Nasal swab for potential viral pathogens
  - Sputum culture, blood culture, and urine culture
  - Pulmonary and infectious disease consultation, consider PFTs
  - Bronchoscopy with BAL to rule out infection and malignant lung infiltration
  - Consider empiric antibiotics if infection has not yet been fully excluded
  - Methylprednisolone 1–2 mg/kg/day. Assess response within 48 hours and plan taper over 26 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
    - Mycophenolate mofetil 1–1.5g BID then taper in consultation with pulmonary service
    - Intravenous immunoglobulin (IVIG)

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**Notes**

- a: Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging as ground-glass opacities).
- G3-severe symptoms involve all lung lobes or >90% of lung parenchyma, limiting self-care ADL; G4-life-threatening respiratory compromise.
- See Principles of Immunosuppression (IMMUNO-A).
- See Principles of Immunotherapy Rechallenge (IMMUNO-G).
- Total dosing should be 2 g/kg, administered in divided doses per package insert.
Figure 1. Pneumonitis. Chest computed tomography scans of a 72-year-old male with stage IV lung adenocarcinoma on second-line nivolumab. (A): After three cycles. (B): Grade 1 cryptogenic organizing pneumonia-like pneumonitis after eight cycles. (C): Improvement after 4 weeks of steroids and holding nivolumab; then steroids were tapered slowly over 4 more weeks, and nivolumab was restarted. (D): After 10 cycles.
Immune-related hepatotoxicity

• Hepatitis occurs in 5%–10% (grade 3; 1-2%) in monotherapy and 25%–30% (grade 3; 15%) in combination regimen
• Serum transaminases and bilirubin measured before every cycle of treatment
• Hepatitis is usually asymptomatic and detected on such routine blood monitoring
• Liver biopsy may be considered in assisting in the differential diagnosis of more severe hepatic reactions
• Hepatitis usually resolves within 4–6 weeks with appropriate treatment but in the event that it does not resolve, other contributory causes should be reconsidered and the initial diagnostic work repeated as necessary
Management of Immune Checkpoint Inhibitor-Related Toxicities

HEPATIC ADVERSE EVENT(S)  ASSESSMENT/GRAINING  MANAGEMENT

Transaminitis without elevated bilirubin

- Rule out viral etiology, disease-related hepatic dysfunction, other drug-induced transaminase elevations
- Consider GI evaluation
- Ultrasound
- Consider magnetic resonance cholangiopancreatography (MRCP) if normal ultrasound
- Limit/discontinue hepatotoxic medications (assess acetaminophen, dietary supplement, and alcohol use)

Mild (G1)  ≤ 3 × ULN
- Continue immunotherapy, consider holding immunotherapy for concerning lab value trend
- Assess transaminases and bilirubin with increased frequency

Moderate (G2) 3–5 × ULN
- Hold immunotherapy
- Monitor liver function tests (LFTs) every 3–5 days
- Consider prednisone 0.5–1 mg/kg/day

Severe (G3)  >5–20 × ULN
- Permanently discontinue immunotherapy
- Initiate prednisone 1–2 mg/kg/day
- Consider inpatient care
- Monitor liver enzymes every 1–2 days
- Hepatology consultation
- If steroid refractory or no improvement after 3 days, consider adding mycophenolate
- Infliximab should not be used for hepatitis

Grade >1 transaminitis with bilirubin

- Life-threatening (G4)  >20 × ULN
- Permanently discontinue immunotherapy
- Initiate prednisone/methylprednisolone 2 mg/kg/day
- Inpatient care
- Monitor liver enzymes daily
- Hepatology consultation
- Liver biopsy if no contraindications
- If steroid refractory or no improvement after 3 days, consider adding mycophenolate
- Infliximab should not be used for hepatitis

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

- One-third of patients have diarrhea, while the frequency of colitis: 8%-22%
- GI toxicity is one of the most frequent and severe of irAEs associated with anti-CTLA4
- Colon perforation: 1%-1.5% of melanoma patients receiving ipilimumab
- **Onset** - any time during 1-10 infusions of anti-CTLA4, enterocolitis may even occur several months after last dose of ipilimumab
- Endoscopic lesions of the colon are often extensive and may extend proximal to the sigmoid colon in two thirds of cases.
- Patchy discontinuous endoscopic lesions are observed in half of the patients


NCCN Guidelines Version 1.2019
Management of Immune Checkpoint Inhibitor-Related Toxocities

GASTROINTESTINAL ADVERSE EVENT(S)  ASSESSMENT/GRADING  MANAGEMENT

Mild (G1)\textsuperscript{b}  <4 above baseline per day  • Consider holding immunotherapy\textsuperscript{q}
• Loperamide or diphenoxylate/atropine
• Hydration
• Close monitoring\textsuperscript{h}

• Diarrhea
• Colitis\textsuperscript{a}

Moderate (G2)\textsuperscript{c}  or Severe (G3–4)\textsuperscript{d}  • Stool evaluation to rule out infectious etiology\textsuperscript{e}
  • Nucleic acid amplification tests (NAATs) for GI pathogens/bacterial culture
  • C. difficile
  • Ova & parasites; molecular testing for Giardia and Cryptosporidium spp and E. histolytica; consider microsporidia, Cyclospora/isospora spp
  • Viral pathogens testing when available
  • Based on institutional availability, consider lactoferrin/calprotectin
  • Consider abdominal/pelvic CT with contrast
  • Consider GI consultation
  • Colonoscopy or flexible sigmoidoscopy ± esophagogastroduodenoscopy (EGD) with biopsy

• Hold immunotherapy\textsuperscript{q}
• Prednisone/methylprednisolone\textsuperscript{l} 1 mg/kg/day\textsuperscript{l}
• No response in 2–3 days:
  • Increase dose to 2 mg/kg/day\textsuperscript{l}
  • Consider adding infliximab\textsuperscript{k}

• G3: Discontinue anti-CTLA-4; consider resuming anti-PD-1/PD-L1 after resolution of toxicity\textsuperscript{q}
• G4: Permanently discontinue immunotherapy agent responsible for toxicity\textsuperscript{q}
• Consider inpatient care for provision of supportive care
• Intravenous (IV) methylprednisolone\textsuperscript{l} 2 mg/kg/day\textsuperscript{l}
• No response in 2 days:
  • Continue steroids, consider adding infliximab\textsuperscript{k}
  • If infliximab-refractory, consider vedolizumab

\textsuperscript{a}Symptoms include: watery diarrhea, cramping, urgency, abdominal pain, blood and mucus in the stool, fever. Blood in the stools and/or fever should prompt a more thorough workup for infection and for other causes of GI bleeding, including peptic ulcer disease (PUD) and malignant bleeding.
\textsuperscript{b}Fewer than 4 bowel movements above baseline per day and no colitis symptoms.
\textsuperscript{c}4–6 bowel movements above baseline per day; colitis symptoms, not interfering with ADLs.
\textsuperscript{d}More than 6 bowel movements above baseline per day; colitis symptoms, interfering with ADLs, hemodynamic instability, hospitalization, other serious complications (eg, ischemic bowel, perforation, toxic mega-colon).
\textsuperscript{e}It is not necessary to wait for test results before providing therapy to manage immune-related adverse events (irAEs).
\textsuperscript{f}See Principles of Immunosuppression (IMMUNO-A).
\textsuperscript{g}See Principles of Immunotherapy Rechallenge (IMMUNO-C).
\textsuperscript{h}If progressive, consider stool evaluation to rule out infectious etiology.
\textsuperscript{i}Consider inpatient care when appropriate.
\textsuperscript{j}Treat until symptoms improve to Grade ≤ 1 then taper over 4–6 weeks.
\textsuperscript{k}Duration of therapy with tumor necrosis factor alpha (TNF- alpha) blockers is not clearly defined, but is usually a single dose. Repeat endoscopy may be helpful, but optional for the guidance of treatment. (See Principles of Immunosuppression [IMMUNO-A] regarding TB testing.)
Neurological toxicity

- The incidence - 1%, the time to onset varied from 6 to 13 weeks
- More frequent with CTLA4 then PD1/PDL1
- Range of neurological events:
  - PD1: myasthenia gravis
  - CTLA4: polyneuropathy, GBS, posterior reversible leukoencephalopathy, transverse myelitis, enteric neuropathy, encephalitis and aseptic meningitis
- Investigation: imaging of the CNS, nerve conduction studies and lumbar puncture
- Treatment: corticosteroid plasmapheresis or Immunoglobulin in MG or GBS
Cardiac toxicity

• The incidence <1%, Range of toxicities: myocarditis, pericarditis, arrhythmias, cardiomyopathy and impaired ventricular function
• The incidence is higher with the combination of ipi and nivo (0.27%) compared with nivolumab alone (0.06%)
• When a myocarditis is suspected, admit the patient and immediately start high-dose (methyl)prednisone (1–2mg/kg)
• In the case of deterioration, consider adding another immunosuppressive drug (anti-TNF or MMF)
Renal toxicity

- Incidence <1%, much higher with combination of ipi/nivo, reaching 4.9%, with 1.7% of grade 3-4 toxicity
- Serum Na, K, BUN and Cr should be measured before every infusion
- In case of nephritis, rule out other causes of renal failure first
- Interrupt or permanently discontinue ICI depending on the severity of the renal insufficiency, (methyl)prednisone 1–2mg/kg/day
- Renal biopsy - acute tubulo-interstitial nephritis with lymphocytic infiltration was the most frequent finding
## PRINCIPLES OF ROUTINE MONITORING

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

- It is important to take history of any autoimmune disease
- Record all medications and herbal supplements
- **Reproductive age**: use effective birth control during and for at least 5 months after the final dose of ICI
- The effect of ICI on reproductive function is unknown
- Consider fertility preservation for all patients who have not yet completed family planning
- **Breastfeeding** is contraindicated during ICI
- **Vaccines** that are activated or killed preparations are permissible during ICI. Live vaccine is not recommend
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 is important to prevent the recurrence of irAEs. Choose the right dose (1mg/kg/day) and start early, taper slowly over 6-8 weeks. Severe or steroid-refractory irAEs may require additional immunosuppressive agents. Recommendation for use of specific immune-modulating agents to manage irAEs are typically extrapolated from evidence for treating autoimmune conditions.
PRINCIPLES OF IMMUNOSUPPRESSION

- These immunosuppression recommendations are for patients receiving immune checkpoint inhibitor immunotherapy.
- 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.
  - Corticosteroids are the mainstay of treatment of most irAEs related to immunotherapy.
  - Early intervention with corticosteroids is a key goal in general management of immune-related toxicity.
  - Use of corticosteroids to treat irAEs has NOT been shown to reduce anti-tumor efficacy.
  - In the absence of specific indications such as prior infusion reaction or concurrent chemotherapy, routine premedication with corticosteroids is not recommended given the potential mitigation of immunotherapeutic effectiveness in the prophylactic setting.
  - Longer steroid tapers (>4 weeks, sometimes 6–8 weeks or longer) may be required to prevent recurrent irAE events, particularly pneumonitis and hepatitis.
  - 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.
- Prophylaxis against pneumocystis jiroveci pneumonia (PJP) can be considered in patients receiving a prednisone equivalent of 20 mg or more daily for 4 or more weeks.
- Prophylaxis against fungal infections (eg, fluconazole) can be considered in patients receiving a prednisone equivalent of 20 mg or more daily for 6–8 or more weeks.
- Prophylaxis against herpes zoster reactivation can be considered.
- Proton pump inhibitor therapy or H2 blockers can be considered for patients at higher risk of gastritis (eg, NSAID use, anticoagulation) for the duration of corticosteroid therapy.
- Higher potency (eg, Class 2 or 3) topical corticosteroids are preferred for short-term use for immune-related dermatitis, compared to longer term use of lower potency steroids.
- For neurologic, cardiac, or grade 3 or 4 irAEs, higher dose steroids (eg, methylprednisolone or prednisone 1–2 mg/kg/day) should be given.
TNF inhibitors: Infliximab

- Blocks the interaction of TNF-α with its receptors, inhibiting induction of pro-inflammatory cytokine (IL-1, IL-6) and modulating the activity of immune effectors such as leukocytes and eosinophils
- For patients with severe irAEs not responsive to steroid within 48-72 hrs
- Duration of infliximab – not clearly defined, but typically a single dose
- A second dose can be administered 2 weeks after initial dose
- Effective in immune-related colitis and inflammatory arthritis
- Infliximab has hepatic and neurological toxicity hence do not use if those are suspected
Importantly, so far there is no evidence that the clinical outcome of patients on ICI is affected by the use of immunosuppressive agents for the management of immune-related toxicities.
**General principles of Immunosuppression**

**Mycophenolate-containing medicine:**
- Preventing organ rejection after transplant
- Mycophenolic acid (MPA) or mycophenolate mofetil (MMF)
- MOA: decrease B- and T-cell proliferation, T-cell apoptosis, and suppression of dendritic cells and IL-1
- Use in steroid-refractory irAEs: liver, kidney, pancreas and eyes

**Other treatments**
- Intravenous immunoglobulin (IVIG) or Plasmapheresis – often indicated as second line therapy for neurologic irAES after non-response to high dose steroid
- Cyclophosphamide, cyclosporin, methotrexate and antirheumatic agents (eg, sulfasalazine)
Patients with pre-existing autoimmune conditions or organ transplant recipients may be candidates for immune checkpoint blockade.

- Anti-CTLA-4-based therapy has a higher incidence of exacerbating baseline autoimmune conditions relative to anti-PD-1/PD-L1-based approaches.
- Optimization of immunosuppression for pre-existing autoimmune conditions, including close follow-up with pertinent subspecialists, is recommended.
  - Goal of immunosuppressive regimen allowing for dose of prednisone <10 mg daily or equivalent prior to initiating cancer immunotherapy.
- Graft failure while on cancer immunotherapy has been reported. Transplant organ loss may be an outcome of treatment with cancer immunotherapy and should be discussed with patient and organ transplant team.
  - Patients with solid organ transplantation who have viable option for alternative therapy if graft rejection (eg, kidney) may be candidates for immunotherapy, particularly if no prior evidence of graft rejection and if on maintenance immunosuppression.
- Patients with autoimmune neurologic conditions or life-threatening autoimmune disorders, particularly if not controlled with immunosuppressive medications or requiring high doses of immunosuppression, are unlikely to be suitable candidates for cancer immunotherapy.
- Patients with prior allogeneic stem cell transplant may be candidates for immunotherapy.
  - There is an increased risk of transplant-related complications, including potentially fatal graft-versus-host disease (GVHD).
  - Careful discussion with patient and stem cell transplant physicians should precede initiation of immunotherapy.

Patients with history of HIV or viral hepatitis may be candidates for immunotherapy.

- 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.
TAKE HOME MESSAGE

- Immune checkpoint blockade can lead to the breakdown of immune-tolerance, thereby inducing autoimmune/auto-inflammatory side effects.
- irAEs can affect various organs in host ranging from mild to life-threatening.
- Frequency, duration, and onset vary between classes of ICIs.
- Serious irAEs will increase in frequency and severity as immunotherapeutic approaches become more effective.
- We need better insight on the effect of ICIs on normal tissues, so that potential irAEs can be predicted based on their selectivity profile.
TAKE HOME MESSAGES

Patient education is essential

Multidisciplinary approach is also essential in monitoring patients

A formal monitoring plan should be established in the clinic in order to follow these patients