Immuno-Oncology: Essentials for Nurses in Cancer Care

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Acknowledgements

Adapted from: The Complete Immuno-Oncology Essentials for Oncology Nurses Educational Series (2017)
Objectives

- Review immune system and its functioning
- Describe the differences between immuno-oncology and traditional cancer therapies
- Review current and pending immuno-oncology agents

Outline the Nurses role in Immuno-oncology practice:
- Patient assessment: hx, medications, treatment side effects
- Early identification and management of toxicities
- Patient education

- Review Immune Related Adverse Events
History of Immunotherapy

First use of immunotherapy to control disease
First connection between inflammation and cancer
First demonstration that bacterial products had benefits for inoperable cancers
Proposal that immune system suppresses tumour formation, identified in 1950s as "immune surveillance"
Discovery of dendritic cell
Technology to generate monoclonal antibodies developed
First human testing of biological therapy for cancer
Blockade of immune checkpoints in mouse model of cancer


Approvals and new developments of various I-O therapies including cytokines, tumour-directed monoclonal antibodies, vaccines, and immune checkpoint inhibitors
Why Immuno-oncology?

Long-Term Survival Remains a Challenge in Advanced Cancers

Five-year survival remains poor for many patients with metastatic solid tumours (US, 2007-2013)

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>3%</td>
</tr>
<tr>
<td>Lung</td>
<td>4%</td>
</tr>
<tr>
<td>Bladder</td>
<td>5%</td>
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<tr>
<td>Kidney/Renal</td>
<td>12%</td>
</tr>
<tr>
<td>Colorectal</td>
<td>14%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>20%</td>
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</tbody>
</table>

UNMET NEED
Therapies that offer long-term survival benefits, and that maintain quality of life
Immuno-Oncology - How it’s different?

How Is Immuno-Oncology Different From Other Types of Cancer Treatment?

- **Immuno-Oncology** uses drugs called cancer immunotherapies to activate cells of your immune system that attack cancer cells.
  - But it might also harm healthy cells.

- **Chemotherapy** uses drugs to attack rapidly dividing cells, like cancer cells.
  - However, it might also injure healthy cells that are rapidly dividing.

- **Targeted therapy** uses drugs to attack cancer cells more specifically than chemotherapy.
  - Still, targeted therapy might damage healthy cells.

- **Radiation therapy** uses beams of intense energy to target the cancer site.
  - Even with careful planning, this therapy can still hurt healthy cells.
New Treatment Modalities Are Needed

- Traditional therapies for advanced cancer, including surgery, radiation, and cytotoxic therapy, **target the tumour**
- Cancer immunotherapy or immuno-oncology (I-O) harnesses the body’s own immune system to fight cancer
Overview of the Immune System

External threats: viruses, parasites, protozoa, fungi, bacteria, toxins
Internal threats: cancer

Innate Immunity
- Immediate
- First line of immune defense
- Nonspecific response

Adaptive Immunity
- Slow response
- Antigen-specific response
- Memory
Key Players in the Immune System

**Antigens**
- Abnormal cell substances/proteins which can be recognized and responded to by the immune system

**Antigen-presenting cells (APC)**
- Take up **antigens** from infected or malignant cells and process them into shorter peptide segments
- Present antigen to **T cells** to mobilize an immune response

**T cells**
- Have **T-cell receptors**, which can recognize tumour-associated antigens
- Play a major role in killing infected or malignant cells when activated
- Help perpetuate ongoing immune responses
Key Players in the Immune System

**B cells**
- Display B-cell receptors, which can bind free-floating antigens in the blood or lymph
- Once activated, B cells differentiate to become plasma cells which can secrete large quantities of **antibodies** against a specific antigen

**Antibodies**
- Are secreted by **activated B cells**, called plasma cells
- Tag antigen-containing cells for attack by other parts of the immune system, or neutralize their targets directly by blocking important mechanisms

**NK cells**
- Can recognize infected or **malignant cells** innately without contact with an antigen-presenting cell or antibody (allows NK cells to launch rapid responses against stressed cells)
- Can also attack based on recognition of antibodies on a cell surface
Specific Adaptive Immune Response Against Cancer

**Humoral immunity**
- Plasma cells produce antibodies against antigen
- Antibodies tag tumour cells for destruction by other cells and elimination
- Tumour cells express a multitude of proteins, known as tumour-associated antigens
- Apoptosis

**Cell-mediated immunity**
- Naive T cell
  - Activated APC presents the antigen to the T cell along with a costimulatory signal
  - Activated T cell
    - Proliferation and differentiation into effector and memory T cells
    - Cytotoxic T cells migrate to attack and eliminate tumour antigens
- Memory T cell
- NK cell

- B cells recognize antigen
- APCs recognize antigen
- Memory B cell
- Proliferation and differentiation into Plasma and memory B cells

# Types of Immunotherapy

<table>
<thead>
<tr>
<th>ACTIVE</th>
<th>PASSIVE</th>
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</table>
| **Engages the immune system**  
- Acts directly on the body’s own immune system to elicit an immune response to fight cancer | **Enhances pre-existing immune response**  
- Acts on the tumour, in some cases using immune-based mechanisms to fight cancer, but they do not require the patient’s own immune system to initiate a response |
| Durable | Short-lived |
| **Examples:**  
- Therapeutic cancer vaccines  
- Checkpoint inhibitors | **Examples:**  
- Cytokines  
- Tumour-directed monoclonal antibodies |
Cancer and the Immune System

1. **Cancer Immuno-editing**: not all cancer cells are detected and/or eliminated by immune system. Some persist, enter a “dormant” phase, avoid immune detection and then later “escape” as clinically apparent disease.

2. Cancer cells will create an immunosuppressive environment that prevents anti-tumor response from immune system:
   1) will release their own immunosuppressive factors
   2) try to de-regulate the activity of the T-cells
   3) reduce or alter their own cancer antigens
Immune Checkpoints

The immune response is very complex and is highly regulated by the T-cells at “checkpoints”

Immune checkpoints sense when it is to turn down or turn off the immune response

Checkpoint inhibitors are designed to prevent this from occurring, thus allowing enhanced t-cell activation against a cancer cell.
Immune Checkpoint Inhibitors

- **CTLA-4 Inhibitors:**
  - Cytotoxic T-lymphocyte associated antigen
  - CTLA-4 is a checkpoint protein on T-cells
  - Cancer cell proteins will bind to this to prevent it from working
  - CTLA- inhibitors prevent or block this process

- **PD-1 and PD-L1:**
  - Programmed Death and Programmed Death Ligand 1
  - PD-1 present on T-cells, PD-L1 exist on the tumor cells
  - PD-L1 tries to block PD-1 from functioning
  - PD-1 and PD-L1 inhibitors are designed to prevent this process from occurring
# Immune Checkpoint Inhibitors and Indications Currently Available in Canada

<table>
<thead>
<tr>
<th>Agent</th>
<th>Advanced Melanoma</th>
<th>Advanced NSCLC</th>
<th>Advanced RCC</th>
<th>Advanced SCCHN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CTLA-4 inhibitor</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Ipilimumab</td>
<td>1st-line monotherapy</td>
<td>1st-line in combination with nivolumab</td>
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<tr>
<td><strong>PD-1 inhibitors</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Pembrolizumab</td>
<td>1st-line monotherapy in BRAF wild-type</td>
<td>2nd-line in ≥1% PD-L1+ tumours</td>
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<tr>
<td></td>
<td>2nd-line (following progression on ipilimumab and BRAF inhibitor if BRAF V600 mutation positive)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Nivolumab</td>
<td>1st-line monotherapy in BRAF wild-type and BRAF V600 mutation positive</td>
<td>2nd-line (all comers)</td>
<td>2nd-line</td>
<td>2nd-line</td>
</tr>
</tbody>
</table>
### Emerging Indications and Agents (Recent FDA Approvals)

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<tr>
<th>Agent</th>
<th>Advanced Melanoma</th>
<th>Advanced NSCLC</th>
<th>Advanced RCC</th>
<th>Advanced SCCHN</th>
<th>Advanced Bladder</th>
<th>Hodgkin’s Lymphoma</th>
<th>MSI-H</th>
<th>Merkel cell carcinoma</th>
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<tr>
<td>CTLA-4 inhibitors</td>
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<tr>
<td>Ipilimumab</td>
<td>1st-line monotherapy</td>
<td>1st-line in combination with nivolumab</td>
<td>Adjunct setting (FDA)</td>
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<tr>
<td>PD-1 inhibitors</td>
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<td>2nd-line in ≥1% PD-L1+ tumours</td>
<td>2nd-line (FDA)</td>
<td>2nd-line (FDA)</td>
<td>Adult/pediatric patients with refractory CHI, or relapsed after ≥3 prior lines of therapy (FDA)</td>
<td>2nd-line in advanced solid tumours, colorectal cancer with MSI-H or mismatch repair deficient (FDA)</td>
<td></td>
</tr>
<tr>
<td>Nivolumab</td>
<td>1st-line monotherapy in BRAF wild-type and BRAF V600 mutation positive</td>
<td>1st-line in combination with ipilimumab</td>
<td>2nd-line (all comers)</td>
<td>2nd-line</td>
<td>2nd-line (FDA)</td>
<td>Adults patients that relapsed or progressed after HSCT and brentuximab + ≥3 prior lines of therapy (FDA)</td>
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<tr>
<td>PD-L1 inhibitors</td>
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<tr>
<td>Atezolizumab</td>
<td>2nd-line (FDA)</td>
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<tr>
<td>Durvalumab</td>
<td>2nd-line (FDA)</td>
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<tr>
<td>Avelumab</td>
<td>2nd-line (FDA)</td>
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PD-L1 Testing

- NSCLCs tested for PD-L1
- If known metastasis at time of diagnosis, testing automatically completed
- Local testing sent to ON
- 30 – 40 % of NSCLCs will have > 50% PD-L1 expression
- > 50 % eligible for immuno-oncology agent up-front
Some more differences

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy</th>
<th>Immuno-Oncology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attacks tumours or cancer cells directly</td>
<td>Activates the immune response</td>
<td></td>
</tr>
<tr>
<td>Tumours may shrink immediately</td>
<td>Tumours shrink but this may take longer, and may grow before they get smaller (pseudo-progression)</td>
<td></td>
</tr>
<tr>
<td>Attacks all rapidly dividing cells, both healthy and cancerous cells</td>
<td>Overactive immune system results in immune-related side effects</td>
<td></td>
</tr>
<tr>
<td>Works as long as the drug is in the system</td>
<td>May help the immune system long after treatment ends; durable response</td>
<td></td>
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</tbody>
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Pseudo–Progression

- Tumor growth noted before the tumor actually shrinks
- This occurs as a result of early, proliferative immune activity on the tumor: t cell proliferation and stimulation
- Noted early with treatment and monitoring: within first 3-6 months of treatment or 1st or 2nd CT scans for monitoring
- Patient status, clinical exam, toxicity assessment key
- Continue therapy if patient tolerating well
I-O Therapy Takes Time

Multi-Step Process

<table>
<thead>
<tr>
<th>I-O Start</th>
<th>Immune cell activation and proliferation</th>
<th>Effect on tumour</th>
<th>Effect on survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Days to Weeks</td>
<td>Several Weeks</td>
<td>Several Months</td>
</tr>
<tr>
<td>Initial I-O therapy administration</td>
<td>Immune activation; T-cell proliferation starts early on after initial I-O administration</td>
<td>Clinically measurable immune-mediated antitumour effects occur over weeks to months</td>
<td>Potential effect on survival may occur several months after initial I-O administration</td>
</tr>
</tbody>
</table>
Immune Related Adverse Events

Immune-Related Adverse Effects

- Tumour cells arise from normal cells in our body; so some tumour-associated antigens may also be associated with normal, healthy cells.
- By ‘activating’ the immune system with I-O therapy, a major concern is that the immune system will attack normal, healthy cells along with tumour cells.

T cell recognizes tumour-associated antigen on the tumour and attacks.

T cell recognizes tumour-associated antigen on a normal cell and attacks.
Immune Related Adverse Events

The inflammation from I-O therapy can occur just about anywhere in the body; any place that can be inflamed can be targeted by your own immune system.

- I-O therapy–associated AEs include:
  - Skin toxicity
  - Gastrointestinal; colitis
  - Hepatitis
  - Endocrinopathy
  - Neurotoxicity
  - Pneumonitis
  - Nephrotoxicity
Adverse Events - Where?

Remember – anything that can have an “itis” may occur

**Skin**
- Dermatitis, erythroderma
- Erythema multiforme
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis
- Psoriasis
- Vitiligo
- Alopecia

**Eye**
- Conjunctivitis
- Uveitis, iritis, retinitis
- Scleritis, episcleritis
- Blepharitis

**Endocrine**
- Hypo or hyperthyroidism
- Hypophysitis, hypopituitarism
- Adrenal insufficiency
- Type 1 diabetes

**Cardiovascular**
- Myocarditis
- Pericarditis
- Vasculitis

**Hepatic**
- Hepatitis

**Renal**
- Nephritis
- Lupus-like glomerulonephritis

**Neurologic**
- Neuropathy
- Myelopathy
- Guillain-Barre syndrome
- Myasthenia gravis-like syndrome
- Encephalitis, meningitis

**Pulmonary**
- Pneumonitis
- Pleuritis
- Interstitial lung disease

**Gastrointestinal**
- Colitis
- Ileitis
- Pancreatitis
- Gastritis
- GI perforation

**Musculoskeletal**
- Arthralgia, arthritis
- Myalgia, myositis
## Most Common Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Anti-CDL4: Ipilimumab (All Grades)</th>
<th>Anti PD-1/PD-L1: Nivolumab &amp; Pembrolizumab (All Grades)</th>
<th>Combination Therapy (All Grades)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin:</strong> Rash, Pruritis</td>
<td>19%, 24%</td>
<td>21%, 23%</td>
<td>28%, 33%</td>
</tr>
<tr>
<td><strong>Gastrointestinal:</strong> diarrhea, colitis, nausea</td>
<td>28%, 8%</td>
<td>20%, 2%, 26%</td>
<td>37%, 12%, 22%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19%</td>
<td>25%</td>
<td>30%</td>
</tr>
<tr>
<td>Hepatic</td>
<td>3%</td>
<td>4%</td>
<td>16%</td>
</tr>
<tr>
<td>Endocrine</td>
<td>6%</td>
<td>5%</td>
<td>7%</td>
</tr>
</tbody>
</table>
Adverse Events – When?

Overall Appearance of irAEs

- irAEs usually take several weeks to months to occur (typically peak between 4–12 weeks)
- irAEs associated with combination therapy may occur earlier, even a few days after treatment administration
- The majority of irAEs occur in the first few months of treatment
Implications for Nursing
1. Baseline Assessment

Use as a reference for any clinical, biological, or imaging abnormality occurring during or after I-O treatment

- **Medical history**
  - Specific questions on organ function and pre-existing symptoms, such as:
    - History of rash?
    - Bowel function?
    - Coughing or shortness of breath?
    - Nausea or headaches?
    - Previous history of autoimmune disease?
    - Previous infections or risk for infections such as HIV or viral hepatitis?

- **Physical examination**
  - Vital signs (HR, BP, etc.; with oximetry when clinically indicated), weight, other significant findings

- **Laboratory investigations**
  - Routine testing, complete blood count (CBC), biochemistry, renal function, liver function tests (LFTs), thyroid stimulating hormone (TSH), etc.

- **Concomitant drug toxicity profiles**
  - Record and monitor all prescription and nonprescription medications, including vitamins and herbal supplements

- **Imaging**
  - Could consider chest X-ray or thoracic CT when clinically indicated

Continue to closely follow patient
Nursing Assessment: Follow-up

- Early diagnosis and appropriate management are essential
  - Review of signs and symptoms, leading to classification as skin reaction (dermatitis), gastrointestinal (enterocolitis), liver (hepatitis), endocrine disorders, lung (pneumonitis), etc.
  - Rule out alternate etiologies (consider differential diagnoses, disease progression, concomitant comorbidities, adverse events caused by other drugs)
  - If the cause is not immune-related, the strategy is to treat the cause and continue immunotherapy
  - If symptoms are immune-related, the strategy is to evaluate severity and determine the intervention
  - It is quite common to start treating an AE as immune-related while ruling out or even starting treatment of alternate etiologies (e.g., starting steroids and antibiotics with a patient who has pneumonitis while ruling out pneumonia)
# Grading Adverse Events

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Asymptomatic or mild symptoms</td>
</tr>
</tbody>
</table>
| Grade 2 | Moderate symptoms  
  Limiting age-appropriate instrumental ADL, such as preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. |
| Grade 3 | Severe but not immediately life-threatening  
  Disabling; limiting self-care ADL, such as bathing, dressing/undressing, feeding self, using the toilet, taking medications, and not bedridden |
| Grade 4 | Life-threatening consequences |
| Grade 5 | Death related to AE |
Management Guidelines for irAEs

Signs and Symptoms Present

No

Rule out alternative etiologies

Yes

Determine severity using NCI-CTCAE grading scale
Management Guidelines for irAEs

Signs and Symptoms Present → Determined Cause and Severity → I-O Therapy

- Rule out alternative etiologies
  - No → Manage with appropriate therapy based on etiology → CONTINUE
  - Yes → irAE?
    - No → Grade 1
    - Yes → Determine severity using NCI-CTCAE grading scale
      - Any grade 2 or some grade 3 (skin/endocrine) toxicities
      - Grade 3-4 toxicity
Management Guidelines for irAEs

Signs and Symptoms Present
- Rule out alternative etiologies
  - No irAE?
    - Yes: Determine severity using NCI-CTCAE grading scale
      - Grade 1
      - Any grade 2 or some grade 3 (skin/endocrine) toxicities
      - Grade 3-4 toxicity
  - Manage with appropriate therapy based on etiology
    - Manage with symptomatic therapy (e.g., antidiarrheal, antihistamine, etc. Refer to organ-specific guidelines)
    - CONTINUE

Determine Cause and Severity
- Adverse Event Management
- I-O Therapy
- CONTINUE
Management Guidelines for irAEs

**signs and symptoms present**
- Rule out alternative etiologies
- Determine severity using NCI-CTCAE grading scale

**Yes**
- Grade 1
  - Manage with appropriate therapy based on etiology
    - Manage with symptomatic therapy (e.g., antidiarrheal, antihistamine, etc. Refer to organ-specific guidelines)
    - CONTINUE
  - Any grade 2 or some grade 3 (skin/endocrine) toxicities
    - Administer oral steroid therapy*
    - Consider organ-specific specialist consult
    - SUSPEND

**No**
- irAE?
  - Continue
  - Improve to grade 1

*e.g., Oral prednisone 1 mg/kg/day, IV methylprednisolone 2 mg/kg/day, or equivalent; depending on the dose/length of time, if symptoms improve, gradually taper over a minimum of 4 weeks
Management Guidelines for irAEs

Signs and Symptoms Present

- Rule out alternative etiologies
  - No irAE?

- Determine severity using NCI-CTCAE grading scale
  - Grade 1
  - Any grade 2 or some grade 3 (skin/endocrine) toxicities
  - Grade 3–4 toxicity

- Determine cause and severity
  - Manage with appropriate therapy based on etiology
    - Manage with symptomatic therapy (e.g., antidiarrheal, antihistamine, etc. Refer to organ-specific guidelines)
    - Improve to ≤ grade 1
    - Continue
    - If no improvement to ≤ grade 1 after 1 week, manage as high-grade event

- Adverse event management

- IO therapy

- Treat with high-dose steroid therapy*
  - Consult organ-specific specialist
  - Discontinue

* e.g., Oral prednisone 1 mg/kg/day, IV methylprednisolone 2 mg/kg/day, or equivalent; depending on the dose/length of time, if symptoms improve, gradually taper over a minimum of 4 weeks
Management Guidelines for irAEs

- **Signs and Symptoms Present**
  - Rule out alternative etiologies
  - Determine severity using NCI-CTCAE grading scale

- **Determining Cause and Severity**
  - Manage with appropriate therapy based on etiology
    - Grade 1
      - Manage with symptomatic therapy (e.g., antidiarrheal, antihistamine, etc. Refer to organ-specific guidelines)
      - Continue
    - Any grade 2 or some grade 3 (skin/endocrine) toxicities
      - Administer oral steroid therapy*
        - Consider organ-specific specialist consult
      - If no improvement to ≤ grade 1 after 1 week, manage as high-grade event
    - Grade 3–4 toxicity
      - Treat with high-dose steroid therapy*
        - Consult organ-specific specialist
      - If no improvement
        - Refer to organ-specific guidelines
          - Consider alternate immunosuppressive therapy (e.g., infliximab or mycophenolate)
          - Administer antimicrobial prophylaxis as appropriate for patients on long-term immunosuppressive therapy.
          - Discontinue

- **Adverse Event Management**
  - Continue

- **I-O Therapy**
  - Continue
  - Improve to ≤ grade 1
  - Suspending
  - Discontinue

*e.g., Oral prednisone 1 mg/kg/day, IV methylprednisolone 2 mg/kg/day, or equivalent; depending on the dose/length of time, if symptoms improve, gradually taper over a minimum of 4 weeks.
Immune Related Adverse Events

Remember – anything that can have an “itis” may occur

**Skin**
- Dermatitis, erythroderma
- Erythema multiforme
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis
- Psoriasis
- Vitiligo
- Alopecia

**Pulmonary**
- Pneumonitis
- Pleuritis
- Interstitial lung disease

**Gastrointestinal**
- Colitis
- Ileitis
- Pancreatitis
- Gastritis
- GI perforation

**Musculoskeletal**
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**Neurologic**
- Neuropathy
- Myelopathy
- Guillain-Barre syndrome
- Myasthenia gravis-like syndrome
- Encephalitis, meningitis
Dermatological irAEs

Incidence
- All grades: ~50% with anti-CTLA-4; 30–40% with anti-PD-1/PD-L1
- Grades 3–4: ~1%

Symptoms
- Itchiness (pruritus)
- Redness (erythema)
- Rash
- Peeling
- Skin excoriations

Assessment
- A good history should be taken to rule out other causes of skin issues
- Important to evaluate and identify alternative etiologies not attributable to I-O therapy (e.g., viral/bacterial infection)
- Evaluate impact on daily activities and sleeping
- Watch for signs of infection
- Consider dermatologic consultation if severe; consider skin biopsy

Symptomatic Treatment
- Skin care, nonirritating moisturizers/emollients, sunscreen
- Avoid irritation (sun exposure, extreme heat)
- Topical therapy (urea-containing creams, topical steroids)
- Oral antihistamines
- Generally reversible
- Encourage patient to contact nurse or physician if rash worsens
Skin irAE Management Algorithm

Rule out noninflammatory causes. If noninflammatory cause, treat accordingly and continue I-O therapy.

**Grade of Rash**
- **Grade 1–2**
  - Covering ≤30% body surface area (BSA)
  - Continue I-O therapy
  - Symptomatic therapy (e.g., topical steroids, oral antihistamines)

**Grade 3–4**
- Covering >30% BSA; Life-threatening symptoms
  - Delay I-O therapy if moderate, discontinue I-O therapy if severe
  - Consider dermatology consult and skin biopsy
  - Consider hospitalization if severe
  - Methylprednisolone 1–2 mg/kg/day or IV equivalent

**Management**

**Follow up**
- If persists >1–2 weeks or recurs:
  - Delay I-O therapy
  - Consider dermatology consult; skin biopsy
  - Consider prednisolone 0.5–1 mg/kg/day or oral equivalent
  - Once improves, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and consider resuming I-O therapy
- If worsens:
  - Treat as grade 3–4
- If improves to grade 1:
  - Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections
  - Consider resuming I-O therapy on a case-by-case basis
  - If no improvement within 48–72 hours:
    - Consider additional immunosuppression (e.g., infliximab)
# Gastrointestinal irAEs

## Incidence
- All grades: 30–40% with anti-CTLA-4; up to 25% with anti-PD-1/PD-L1
- Grades 3–4: 1–5% (up to 10% with combination)

## Symptoms
- Diarrhea
- Constipation
- Abdominal pain/cramping
- Nausea/vomiting
- Blood or mucus in stool
- Inability to eat or drink

## Assessment
- Ask patients to report any bowel habit changes promptly
- Number of bowel movements/day — at baseline and change during follow up
- Check if new drugs prescribed with risk of GI AEs (antibiotics, NSAIDs, ibuprofen, metformin) or for use of laxatives
- Note that opiates/narcotics may mask symptoms of perforation
- Stool culture (*C. difficile*, etc.)
- In patients symptomatic for enterocolitis, rule out infectious etiologies and consider endoscopic evaluation for persistent or severe symptoms
- Consider GI consult if moderate to severe symptoms; consider lower endoscopy

## Symptomatic Treatment
- Adequate oral hydration, electrolyte replacement, diet modification (colitis diet; BRAT diet – bananas, rice, applesauce, toast), and antidiarrheal (loperamide)
- Encourage patient to contact nurse or physician if number of stools increases to 3–4 times per day while on loperamide
# GI irAE Management Algorithm

Rule out noninflammatory causes. If noninflammatory cause, treat accordingly and continue I-O therapy.

<table>
<thead>
<tr>
<th>Grade of Diarrhea/Colitis (NCI CTCAE v4)</th>
<th>Management</th>
<th>Follow up</th>
</tr>
</thead>
</table>
| Grade 1: Increase of <4 stools/day over baseline; mild increase in ostomy output vs. baseline | • Continue I-O therapy  
• Symptomatic treatment (e.g., hydration, diet, loperamide) | • Close monitoring for worsening symptoms  
• Educate patient to report worsening immediately if worsens  
• Treat as higher grade |
| Grade 2: Increase of 4–6 stools/day over baseline; moderate increase in ostomy output vs. baseline  
Abdominal pain; mucus or blood in stool | • Delay I-O therapy  
• Symptomatic treatment (e.g., hydration, diet, etc.) | If improves to grade 1:  
• Resume I-O therapy  
If persists >2–3 days or recurs:  
• Consider GI consult; endoscopy  
• Prednisolone 0.5–1mg/kg/day or oral equivalent  
• Once improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections; consider resuming I-O therapy if worsens or persists >3–5 days with oral steroids:  
• Treat as grade 3–4 |
| Grade 3–4: ≥7 stools per over baseline; incontinence; moderate increase in ostomy output vs. baseline  
Severe abdominal pain, peritoneal signs  
Life-threatening symptoms | • Discontinue I-O therapy  
• Hospitalization, intravenous hydration with electrolyte replacement  
• GI consult; consider lower endoscopy; check *C. difficile* titres and cultures  
• Methylprednisolone 1–2 mg/kg/day or IV equivalent  
• Add prophylactic antibiotics for opportunistic infections | If improves:  
• Continue steroids until grade 1, then taper over at least 1 month  
If persists >3–5 days, or recurs after improvement:  
• Add infliximab 5 mg/kg (if no contraindication);  
Note: Infliximab should not be used in cases of perforation or sepsis |
# Hepatic irAEs

## Incidence
- All grades: <10% monotherapy; 20–30% combination
- Grades 3–4: <3% monotherapy; ~20% combination

## Symptoms
- Jaundice
- Tiredness
- Nausea, vomiting
- Appetite loss
- Abdominal pain
- Mostly asymptomatic elevation of liver enzymes

## Assessment
- Liver function tests (LFTs) at baseline and before each dose of I-O treatment
- Rule out viral or drug-induced causes
- Consider GI/hepatologist consult if severe; consider imaging to rule malignant etiology if severe

## Monitoring
- Increase frequency of monitoring
- Monitor LFTs daily till resolution followed by weekly testing
## Hepatic irAE Management Algorithm

Rule out noninflammatory causes. If noninflammatory cause, treat accordingly and continue I-O therapy.

<table>
<thead>
<tr>
<th>Grade of LFTs (NCI CTCAE v4)</th>
<th>Management</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1</strong>&lt;br&gt;AST/ALT ≤3.0 x ULN and/or bilirubin ≤1.5 x ULN</td>
<td>• Continue I-O therapy</td>
<td>• Continue LFT monitoring if worsens&lt;br&gt;• Treat as higher grade</td>
</tr>
<tr>
<td><strong>Grade 2</strong>&lt;br&gt;AST/ALT &gt;3–5 x ULN and/or bilirubin &gt;1.5–3 x ULN</td>
<td>• Delay I-O therapy&lt;br&gt;• Increase frequency of monitoring to every 3 days</td>
<td>If returns to baseline:&lt;br&gt;• Resume routine monitoring, resume I-O therapy if elevations persist &gt;5–7 days or worsen:&lt;br&gt;• Prednisolone 0.5–1 mg/kg/day or oral equivalent&lt;br&gt;• Once LFTs returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy if elevations persist treat as higher grade</td>
</tr>
<tr>
<td><strong>Grade 3–4</strong>&lt;br&gt;AST/ALT &gt;5 x ULN and/or bilirubin &gt;3 x ULN</td>
<td>• Discontinue I-O therapy&lt;br&gt;• Increase frequency of monitoring to every 1–2 days&lt;br&gt;• Consult GI/hepatologist; consider imaging&lt;br&gt;• Methylprednisolone 1–2 mg/kg/day or IV equivalent**&lt;br&gt;• Add prophylactic antibiotics for opportunistic infections</td>
<td>If returns to grade 2:&lt;br&gt;• Taper steroids over at least 1 month&lt;br&gt;• If does not improve in &gt;3–5 days, worsens or rebounds:&lt;br&gt;• Add mycophenolate mofetil 1 g BID&lt;br&gt;• If no response within an additional 3–5 days, consider other immunosuppressants per local guidelines (infliximab is contraindicated)</td>
</tr>
</tbody>
</table>
Endocrine irAEs

Incidence
- All grades: <15%
- Grades 3-4: <5%

Symptoms
- Hypothyroidism/hyperthyroidism
  - Fatigue, weakness, heart rate or rhythm abnormalities, constipation/diarrhea, cold/heat intolerance, dry skin, sweating, weight gain/weight loss
- Adrenalitis
  - Lack of energy, anorexia, nausea/vomiting, fever, hypotension, hypoglycemia
- Hypophysitis
  - Headache, visual field defects, blurring of vision, impotence, amenorrhea

Assessment
- Monitor patients for signs and symptoms of hypophysitis, adrenal insufficiency (including adrenal crisis), and hyper- or hypothyroidism
- Monitor thyroid function tests and clinical chemistries at the start of treatment, before each dose, and as clinically indicated based on symptoms
- Consider endocrinologist consult; endocrine function tests when indicated:
  - Thyroiditis: if TSH <0.5 x ULN, or >2 x ULN, or consistently out of normal range in subsequent measurements: include free T3 and T4
  - Adrenalitis: if morning serum cortisol abnormal, include ACTH (cosyntropin) stimulation test
  - Hypophysitis: LH/FSH/testosterone, prolactin; consider radiographic pituitary imaging and visual field testing if indicated

Clinical Treatment
- Subclinical hypothyroidism (TSH<10 mIU/L) does not need to be treated
- Can be controlled by hormone replacement therapy (e.g., levothyroxine for thyroid)
Endocrine irAE Management Algorithm

Rule out noninflammatory causes. If noninflammatory cause, treat accordingly and continue I-O therapy.

Endocrine Disorders
(NTI CTCAE v4)

Grade 1–2
Asymptomatic; mild or moderate symptoms; clinical/diagnostic observations

Management
- Consider endocrinology consult; evaluate endocrine function (TSH, cortisol, ACTH, LH, FSH, prolactin, testosterone) as indicated
- Consider radiographic pituitary imaging if indicated (hypophysitis)

If hyper/hypothyroidism or adrenalitis
- Continue I-O therapy
- Treat hyper/hypothyroidism; replace other hormones as needed

If hypophysitis* (abnormal pituitary lab/scan)
- Delay I-O therapy
- Prednisolone 1–2 mg/kg/day or PO equivalent
- Initiate appropriate hormone therapy

Follow up
- Continue monitoring symptoms; lab tests if no abnormal pituitary lab/MRI 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
  - Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component

Grade 3–4
Severe; life-threatening (e.g., adrenal crisis, i.e., severe dehydration, hypotension, and electrolyte imbalance)

If hyper/hypothyroidism
- Continue I-O therapy; treat for hyper or hypothyroidism

If adrenal insufficiency
- Delay or discontinue I-O therapy
- Consult endocrinologist: rule out sepsis
- If in adrenal crisis, stress dose of IV steroids, antibiotics, IV fluids
- If no adrenal crisis, prednisolone 1–2 mg/kg/day or oral equivalent

If hypophysitis (abnormal pituitary lab/scan)
- Discontinue I-O therapy permanently
- Prednisolone 1–2 mg/kg/day or oral equivalent
- Initiate appropriate hormone therapy

If improves:
- Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections
- Consider resuming I-O therapy once symptoms have improved to grade 1 or patient that is stable on hormonal replacement therapy (even grade 3)
Pulmonary irAEs

Incidence
- All grades: 1% with anti-CTLA-4; 5–7% with anti-PD-1/PD-L1
- Grades 3–4: <1%

Symptoms
- Cough
- Shortness of breath/dyspnea (rest or exertion)
- Chest pain
- Fever
- Asymptomatic radiographic changes (infiltrates on imaging)

Assessment
- Pulse oximetry (rest and exertion)
- Chest X-ray and/or CT
- Monitor temperature
- Rule out other etiologies (imaging and pulmonary consultation)
- Consider pulmonary and infectious disease consult
- Consider bronchoscopy, lung biopsy
Pulmonary irAE Management Algorithm

Rule out noninflammatory causes. If noninflammatory cause, treat accordingly and continue I-O therapy.

<table>
<thead>
<tr>
<th>Grade of Pneumonitis (NCI CTCAE v4)</th>
<th>Management</th>
<th>Follow up</th>
</tr>
</thead>
</table>
| Grade 1  
Asymptomatic; radiographic changes only | • Consider delay of I-O therapy  
• Monitor for symptoms every 2–3 days  
• Consider pulmonary and ID consults | • Monitor every 2–3 days and reimage at least every 3 weeks  
If worsens:  
• Treat as higher grade |
| Grade 2  
Mild to moderate new symptoms | • Delay I-O therapy  
• Pulmonary and ID consults; consider bronchoscopy, lung biopsy  
• Monitor symptoms daily, consider hospitalization  
• Prednisolone 1 mg/kg/day or oral equivalent | • Reimage every 1–3 days  
If improved:  
• When symptoms return to near baseline, taper steroids over at least 1 month and consider prophylactic antibiotics; consider resuming I-O therapy per protocol  
If not improving after 2 weeks or worsening:  
• Treat as grade 3–4 |
| Grade 3–4  
Severe new symptoms; new or worsening hypoxia, life-threatening respiratory compromise | • Discontinue I-O therapy  
• Hospitalize; pulmonary and ID consults; consider bronchoscopy, lung biopsy  
• Methylprednisolone 2–4 mg/kg/day or IV equivalent  
• Add prophylactic antibiotics for opportunistic infections | If improves to baseline:  
• Taper steroids over at least 6 weeks  
If not improving after 48 hours or worsening:  
• Add additional immunosuppression (e.g., infliximab, cyclophosphamide, intravenous immunoglobulin, or mycophenolate mofetil) |
# Neurologic irAEs

## Incidence
- Rare (<1%) with both anti-CTLA-4 and anti-PD-1/anti-PD-L1

## Symptoms
- Sensory or motor neuropathy
- Numbness, tingling, pain in hands or feet
- Sensory alterations
- Muscle weakness
- Paresthesia
- Fatigue
- Difficulty waking up

## Assessment
- Monitor signs and symptoms indicative of neuropathy
- Consider neurologist consultation

## Patient Tips
- Encourage your patients to protect themselves from injury if they have numbness in their hands or feet, such as wearing shoes inside and outdoors, removing clutter to prevent falls, no-slip bath mats, testing bath water with a thermometer, wearing gloves when cooking, walking slowly, use of a cane if needed, etc.
Neurologic irAE Management Algorithm

Rule out noninflammatory causes. If noninflammatory cause, treat accordingly and continue I-O therapy.

**Neurological Toxicity (NCI CTCAE v4)**

**Grade 1**
Asymptomatic or mild symptoms

**Management**
- Continue I-O therapy

**Follow up**
- Continue to monitor the patient
  - If worsens:
    - Treat as higher grade

**Grade 2**
Moderate symptoms; limiting instrumental activities of daily living

**Management**
- Delay I-O therapy
- Consider neurologist consultation; treat symptoms per local guidelines
- Consider prednisolone 0.5–1 mg/kg/day or oral equivalent

**Follow up**
- If improves to baseline:
  - Consider resuming I-O therapy when improved to baseline
  - If worsens:
    - Treat as grade 3–4

**Grade 3–4**
Severe symptoms; limiting self-care activities of daily living; life-threatening

**Management**
- Discontinue I-O therapy
- Neurology consult; consider MRI brain, lumbar puncture, nerve conduction, etc.
- Treat symptoms per local guidelines
- Methylprednisolone 1–2 mg/kg/day or IV equivalent
- Add prophylactic antibiotics for opportunistic infections

**Follow up**
- If improves to Grade 2:
  - Taper steroids over at least 1 month
- If worsens or atypical presentation:
  - Consider intravenous immunoglobulin or other immunosuppressive therapies per local guidelines
Renal irAEs

**Incidence**
- Rare (<1%) with both anti-CTLA-4 and anti-PD-1/anti-PD-L1

**Symptoms**
- Decreased urine
- Blood in urine
- Swollen ankles
- Most commonly present with elevations in serum creatinine

**Assessment**
- Kidney function tests; urine analysis
- Monitor serum creatinine
- Consider nephrologist consultation
- Renal biopsy may help distinguish inflammatory versus noninflammatory etiologies
## Renal irAE Management Algorithm

Rule out noninflammatory causes. If noninflammatory cause, treat accordingly and continue I-O therapy.

<table>
<thead>
<tr>
<th>Creatinine Elevation (NCI CTCAE v4)</th>
<th>Management</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1</strong>&lt;br&gt;Creatinine &gt;1–1.5 x baseline but ≤1.5 x ULN</td>
<td>• Continue I-O therapy  &lt;br&gt;• Monitor creatinine weekly</td>
<td><strong>If returns to baseline:</strong>&lt;br&gt;• Resume routine creatinine monitoring  &lt;br&gt;<strong>If worsens:</strong>&lt;br&gt;• Treat as higher grade</td>
</tr>
<tr>
<td><strong>Grade 2–3</strong>&lt;br&gt;Creatinine &gt;1.5 x baseline but &gt;1.5–6 x ULN</td>
<td>• Delay I-O therapy  &lt;br&gt;• Monitor creatinine every 2–3 days  &lt;br&gt;• Consider nephrologist consult; renal biopsy  &lt;br&gt;• Prednisolone 0.5–1 mg/kg/day or oral equivalent</td>
<td><strong>If returns to grade 1:</strong>&lt;br&gt;• Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and consider resuming I-O therapy and routine creatinine monitoring  &lt;br&gt;<strong>If elevations persist &gt;7 days or worsens:</strong>&lt;br&gt;• Treat as grade 4</td>
</tr>
<tr>
<td><strong>Grade 4</strong>&lt;br&gt;Creatinine &gt;6 x ULN</td>
<td>• Discontinue I-O therapy  &lt;br&gt;• Monitor creatinine daily  &lt;br&gt;• Consider nephrologist consult; renal biopsy  &lt;br&gt;• Prednisolone 1–2 mg/kg/day or oral equivalent</td>
<td><strong>If returns to grade 1:</strong>&lt;br&gt;• Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections</td>
</tr>
</tbody>
</table>
Patient and Family Education

- Adverse events are common, but are usually mild to moderate in severity
- Severe adverse events are not frequent but are treatable
- Early recognition of adverse events is essential: report ALL symptoms, even if they appear to be mild, it can quickly become something serious
- Timing of symptoms: typically peak between 4 – 12 weeks; however may occur anytime during treatment; earlier with combination treatment and can even occur after treatment discontinuation/completion
- Reinforce teaching with every clinic visit
Review: Key take home messages

- Side effects for immuno-oncology agents may not present for a number of weeks or may present after therapy has been discontinued or completed.
- Uniques toxicities with i-o agents are common, but are usually mild; serious adverse events are rare.
- Nurses responsible to obtain good history, BPMH, assess with each treatment and identify problems early.
- Most adverse events are easily manageable with early identification and treatment.
- Educate patients to monitor and report ALL symptoms.
- Corticosteroids work extremely well for management of side effects.
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