



CHECKPOINT INHIBITOR TOXICITIES IN THE ED

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OBJECTIVES



1. What are checkpoint inhibitors?



2. Side effect profiles



3. Managing toxicities



INHIBITING THE INHIBITORS

- The immune system has multiple checkpoints
- These are pathways that serve to up-regulate, or down-regulate the immune response
- In healthy people, inhibitor immune checkpoints reduce autoimmunity
- In an individual with cancer, these checkpoints impair the immune mediated clearance of cancer cells
- Cancer cells use the inhibitor checkpoint molecules to evade the immune system
- Therefore by blocking these checkpoints (aka inhibiting the inhibitors) we are helping our immune system to recognize and attack cancer cells
- Current pathways: CTLA-4 and PD-1/PD-2 and PD-L1



CHECKPOINT INHIBITORS

- Checkpoint inhibitors are monoclonal antibodies
- A simple analogy; cancer cells to teenagers with fake IDs, and with their fake IDs they evade detection by bouncers (aka our immune system), and get into the bar
- Checkpoint inhibitors have been designed to affect the interaction between bouncers and underage teenagers
- These drugs effectively swipe their fake IDs, so when the underage teenagers present to the bar, the bouncers are able to redirect them back home.

THE PLAYERS

7 approved for use in Canada
Used in >14 different cancers
4 most common in the red box

Ipilimumab (CTLA-4)

Nivolumab (PD-1)

Pembrolizumab (PD-1)

Atezolizumab (PD-L1)

Durvalumab (PD-L1)

Avelumab (PD-L1)

Cemiplimab (PD-1)

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IMMUNE-RELATED ADVERSE EVENTS

- Immune checkpoint inhibitors have an adverse event profile distinct from that of conventional chemotherapy
- These drugs result in toxicities known as immune-related adverse events (irAEs) which occur as a result of the **enhanced immune-system response**
- Immune related adverse events can involve any organ system, but most commonly effect the **dermatologic, gastrointestinal, endocrine and pulmonary** systems.

TIME OF ONSET

Typically a couple weeks after starting therapy

May present **>6 months** after **stopping** therapy



GASTROINTESTINAL

- Diarrhea is VERY common
- DDx: Diverticulitis, colitis, enterocolitis, IBD and bowel perforation
 - Up to 10% of patients will develop colitis, 1% of those patients = bowel perforation
- Evaluation:
 - Stool studies (r/o infectious cause)
 - Low threshold for CT scan is suspecting colitis/perforation
 - +/- Colonoscopy
- Management:
 - Medical oncology +/- GI involvement
 - If no infectious cause, corticosteroids and loperamide

DERMATOLOGIC

- Rash is VERY common
- Typical rash is a low grade nonspecific diffuse maculopapular rash to vitiligo
- Cases of SJS, TEN, DRESS
- Evaluation:
 - Rule out other cause
 - Consider dermatology consult for biopsy
- Management:
 - Mild rashes may be managed with antihistamines and topical steroids
 - Steroids are indicated for more severe involvement
 - Consider antibiotics if signs of secondary cellulitis

ENDOCRINE

- Endocrinopathies can occur in ~10% of patients on checkpoint inhibitors
- Can present with central, or peripheral failure
- Commonly: hyperthyroidism, hypothyroidism, hypophysitis
- Less common: adrenal insufficiency, T1DM
- Investigation
 - Depends on cause and presenting symptoms
 - TSH, T3/T4, glucose, electrolytes, cortisol
- Treatment
 - Usually require ongoing hormone replacement
 - Treatment with steroids is variable

PULMONARY

- Pneumonitis is defined as non-infectious lung inflammation with interstitial and alveolar infiltrates
- Clinical presentation:
 - Dry, unproductive cough, tachypnea, dyspnea, tachycardia, cyanosis
 - Fever and productive cough are uncommon in autoimmune pneumonitis, more suggestive of an infectious etiology
- Investigation:
 - CXR, sputum, low threshold for CT, bronchoscopy
 - CXR/CT typically shows ground glass opacities or patchy nodular infiltrates, particularly in lower lobes
 - Routine CXR can miss up to 25% of cases of autoimmune pneumonitis
- Management:
 - Low threshold for admission, even if not requiring oxygen
 - Empiric antibiotics if concern for infectious etiology (typical PNA coverage +/- PJP/fungal coverage if immunosuppressed)
 - Steroids

OTHER



Hepatitis



Neurologic (bell's palsy, encephalitis, transverse myelitis, GBS, myasthenia gravis)



Nephritis



Pancreatitis



Hematologic (autoimmune hemolytic anemia, ITP, lymphopenia, acquired hemophilia A, aplastic anemia)



Myocarditis/Pericarditis



Ocular (episcleritis, conjunctivitis, uveitis)

GRADING OF ADVERSE EVENTS

Based on the US National
Cancer Institute grading scale



Grade 1: Mild symptoms. Continue checkpoint inhibitor, close monitoring.



Grade 2: Limiting ADLs. Stop checkpoint inhibitor, close monitoring.



Grade 3: Disabling, limiting all ADLs. Stop checkpoint inhibitor, treat with steroids.



Grade 4: Life-threatening reaction. Stop checkpoint inhibitor, high dose steroids.



Grade 5: Death related to an adverse event.

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WORKUP

Organ System	Work-Up
Gastrointestinal	Routine bloodwork and stool cultures + LFTs Low threshold for CT abdomen
Dermatologic	Grade 2 or higher = derm for biopsy
Endocrine	Routine bloodwork + Glucose + TSH + Cortisol
Pulmonary	Routine bloodwork, CXR, Sputum Low threshold for CT chest*

*Routine GR can miss up to 25% of cases of autoimmune pneumonitis



TREATMENT

- **First line:** corticosteroids
 - This does not appear to affect the anti-tumor effects of checkpoint inhibitors
 - Early initiation has a favorable prognosis
- **Second line:** unclear
 - Depends on the reaction/organ system involved
 - Various other immunosuppressants (ie - TNF-alpha)

GUIDELINES & ADVICE

Immune Checkpoint Inhibitor Side Effect Toolkit

The *Immune Checkpoint Inhibitor Toxicity Management Toolkit* has been designed to help support individuals taking immune checkpoint inhibitor medications. These individuals may experience side effects that require urgent treatment, and this toolkit will help providers determine the best course of action.

The [corresponding guideline](#) describes in detail the side effects patients may experience and how to help manage them.

The materials are divided into two groups, support documents for providers and information documents for individuals taking the medication.

Provider Tools

Patient Tools

Toxicity algorithms:

- [Dermatological Toxicities](#)
- [Diarrhea and Colitis](#)
- [Hypothyroidism](#)
- [Hyperthyroidism](#)
- [Hypophysitis](#)
- [Adrenal Insufficiency](#)

This QR code will take you
directly to the website



A USEFUL TOOLKIT TO NAVIGATE ADVERSE EVENTS RELATED TO CHECKPOINT INHIBITORS

FIGURE 2
Management of Immune-Related Diarrhea/Colitis^{1,4,5,10,13,14,17-19}

Background: It is important to rule out other etiologies that may be responsible for diarrhea, such as *C.difficile* infections. Severe diarrhea has been observed in patients treated with immune therapy. The median time to onset is 6 to 8 weeks for ipilimumab and nivolumab, and 3.4 months for pembrolizumab. Diarrhea/colitis appears to be less frequent with PD-1 blockade than with CTLA-4 blockade.

EXAMPLE TOOLKIT

**DIARRHEA/
COLITIS**

		MANAGEMENT (First rule out infectious causes)				
		Description	Referral	Corticosteroids	Supportive Therapy	Immune Therapy
DIARRHEA/ COLITIS	GRADE 1	<4 stools/day above baseline.	Not required.	Not required.	Initiate loperamide ^f therapy; maintain oral hydration; consider electrolyte supplementation and dietary modifications. ^g	Monitor closely and continue immune therapy.
	GRADE 2	4-6 stools/day above baseline; abdominal pain, mucus or blood in stool.	Refer to a gastroenterologist for flexible sigmoidoscopy or colonoscopy for persistent grade 2 diarrhea (especially if diagnosis is in question) or any grade 3-4 diarrhea. If any chance of perforation avoid colonoscopy and suggest surgical consult.	Consider starting steroids right away (do not need to wait for consult) or if no improvement after 24 hours of loperamide. Start 0.5-1 mg/kg/day PO prednisone ^h until resolution to grade 0-1. Then taper over 2-4 weeks if 0.5 mg/kg and over 4 weeks if 1 mg/kg. If no improvement in 72 hours, treat as grade 3-4.	Start loperamide ^f and monitor after 24 hours; continue if symptoms improved. Consider prednisone if symptoms worsen or no resolution; give oral/IV hydration; consider electrolyte supplementation and dietary modifications. ^g	Withhold therapy until grade 0-1 and on prednisone <7.5 mg/day (CTLA-4) or <10 mg/day (PD-1). Consider discontinuation if no improvement within 12 weeks or inability to reduce steroids.
	GRADE 3	≥7 stools/day above baseline; incontinence, need for hospitalization for IV fluids ≥24hrs.	Refer to a gastroenterologist for flexible sigmoidoscopy or colonoscopy for persistent grade 2 diarrhea (especially if diagnosis is in question) or any grade 3-4 diarrhea. If any chance of perforation avoid colonoscopy and suggest surgical consult.	Start 1-2 mg/kg/day IV methylprednisolone until improvement, then slow taper over ≥4 weeks. If no response after 3 days, give infliximab 5 mg/kg IV once every 2 weeks* (use with caution in grade 4 due to risk of perforation and avoid if contraindicated).	Admit to hospital and initiate IV hydration. Consider empiric antibiotics as per institutional guidelines for patients who present with fever/leukocytosis. Use opioid analgesics with caution due to risk of narcotic bowel.	Permanently discontinue therapy.
	GRADE 4	Grade 3 plus fever, or peritoneal signs consistent with bowel perforation, or ileus; life-threatening.	Suggest surgical consult.			

GENERAL APPROACH

Checkpoint Inhibitor Therapy

- Rule out infection
- Rule out disease progression

Grade 1-2

- Symptomatic treatment
- Oncology follow up

Grade 3-4

- Contact oncology
- Corticosteroids
- Prophylactic antibiotics
- Admission

ED SPECIFIC RESOURCES

FOAMed:

- <https://emcrit.org/ibcc/checkpoint/#algorithm>
- <https://www.emrap.org/episode/emrap2020april/oncologyrounds>

Guidelines:

- Cancer Care Ontario
- American Society of Clinical Oncology

Literature:

- **Challenge of immune-mediated adverse reactions in the emergency department.** Daniels GA, et al. Emerg Med J 2019;36:369–377. doi:10.1136/emmermed-2018-208206
- **Management of immune checkpoint inhibitor toxicities: a review and clinical guideline for emergency physicians.** Hryniewicki et al. Journal of Emergency Medicine, Vol. 55, No. 4, pp. 489–502, 2018. <https://doi.org/10.1016/j.jemermed.2018.07.005>

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