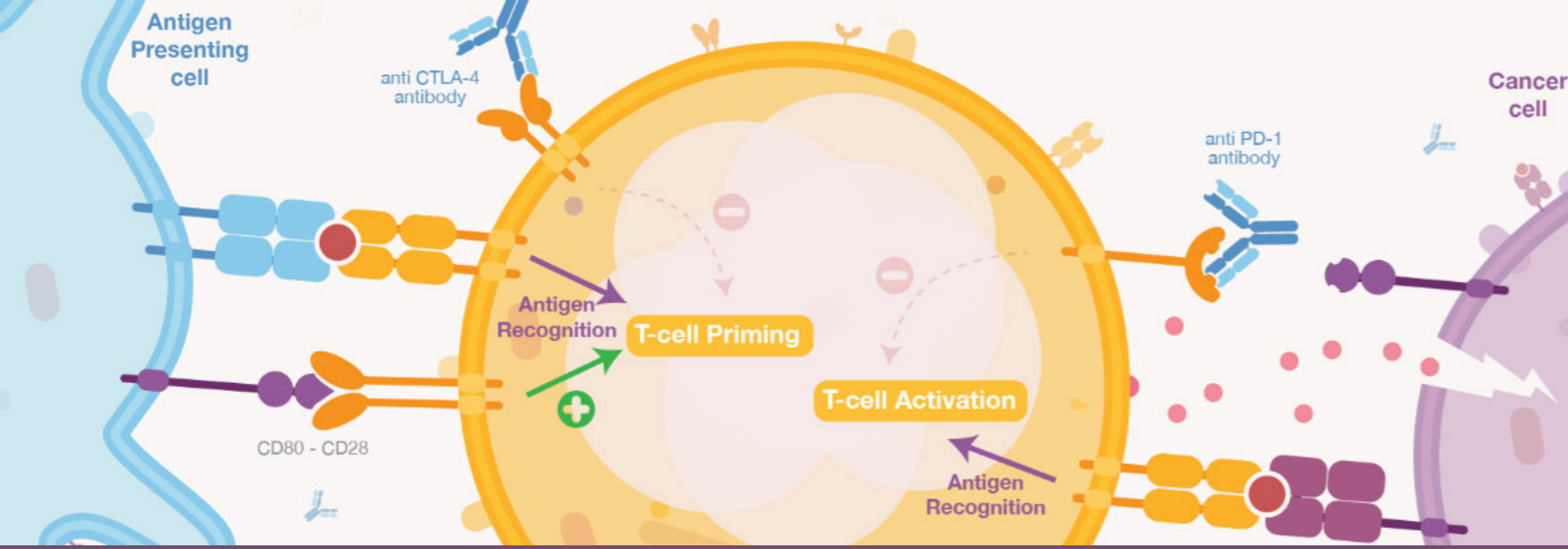

CHECKPOINT INHIBITOR TOXICITIES IN THE ED

Meaghan MacKenzie

R2 Emergency Medicine

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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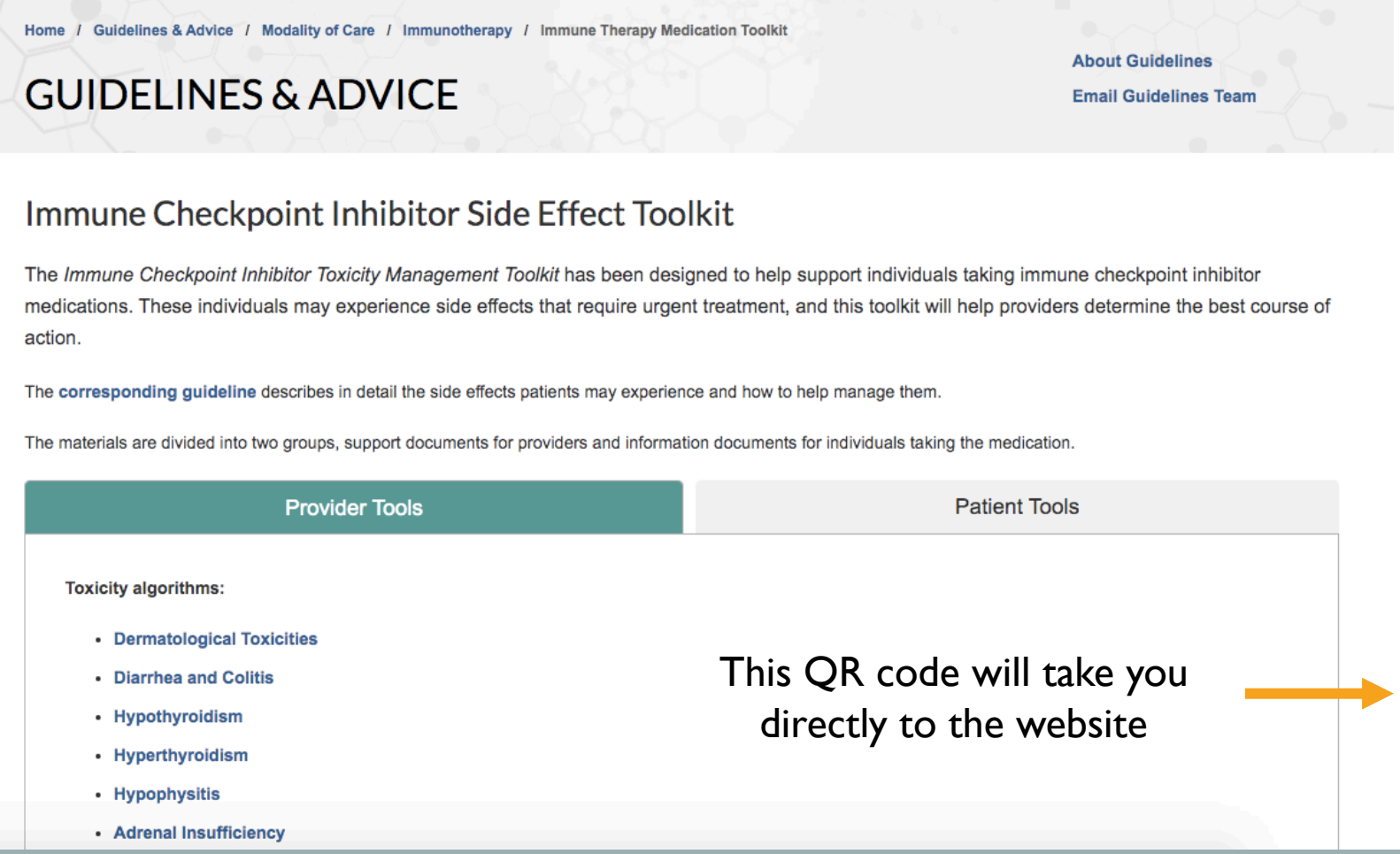
WORKUP

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)



This QR code will take you directly to the website

A USEFUL TOOLKIT TO NAVIGATE ADVERSE EVENTS RELATED TO CHECKPOINT INHIBITORS

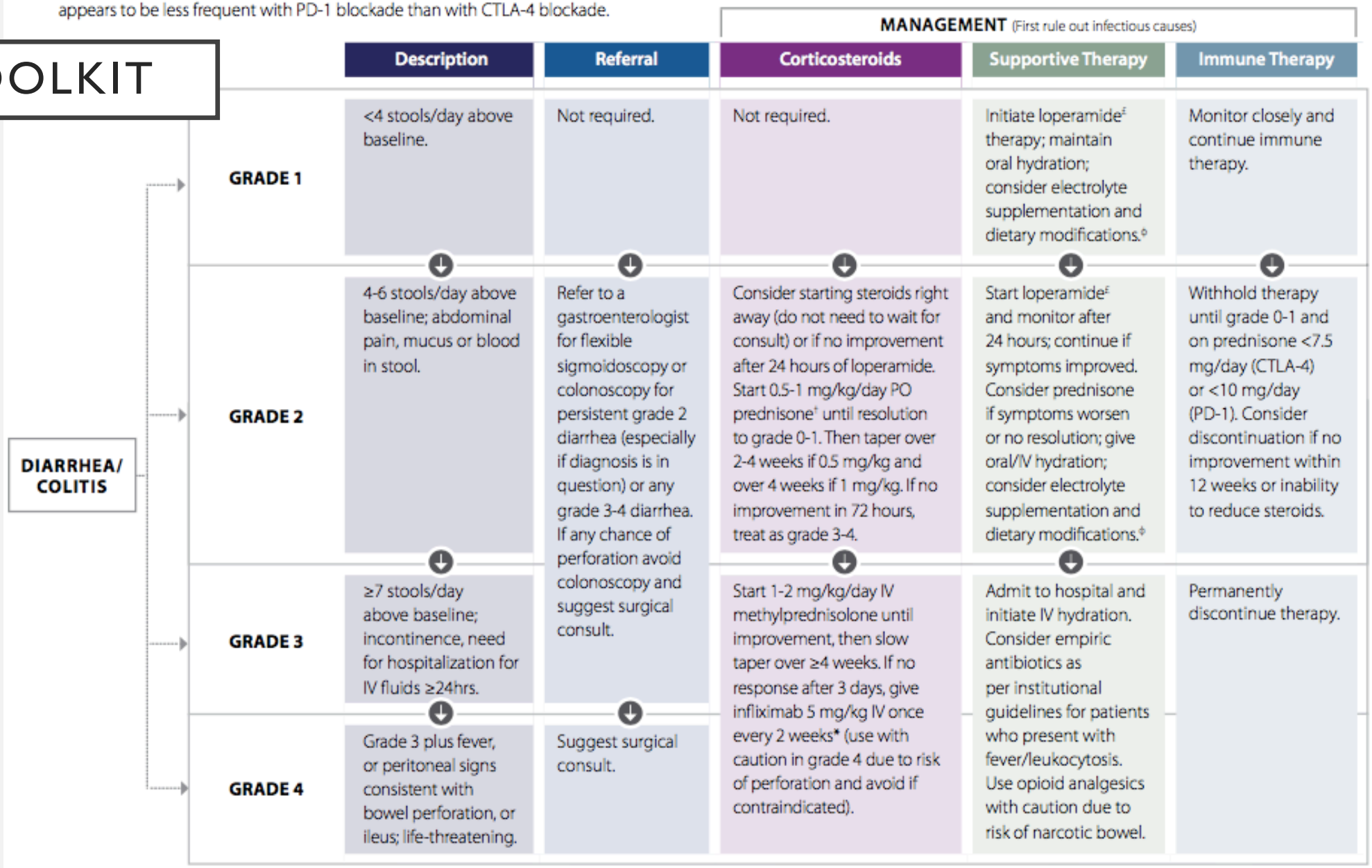
Cancer Care Ontario. Immune Checkpoint Inhibitor Side Effect Toolkit.

EXAMPLE TOOLKIT

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.



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/emermed-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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