

ADVANCES IN  
**Cancer**  
IMMUNOTHERAPY™



# Nursing Perspective on irAEs: Patient Education, Monitoring and Management

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# Disclosures

- No relevant financial relationships to disclose
- I *will not* be discussing non-FDA approved indications during my presentation.

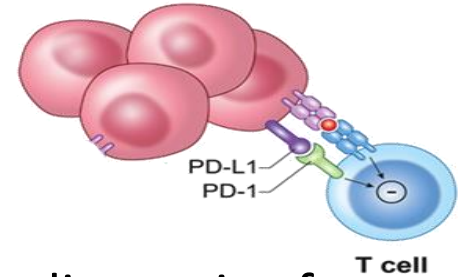


## Objectives

- Improve the early recognition, education and management of immune-related side effects in cancer immunotherapy patients
- Identify strategies for the management of toxicities
- Determine key points for patient education on the management of side effects



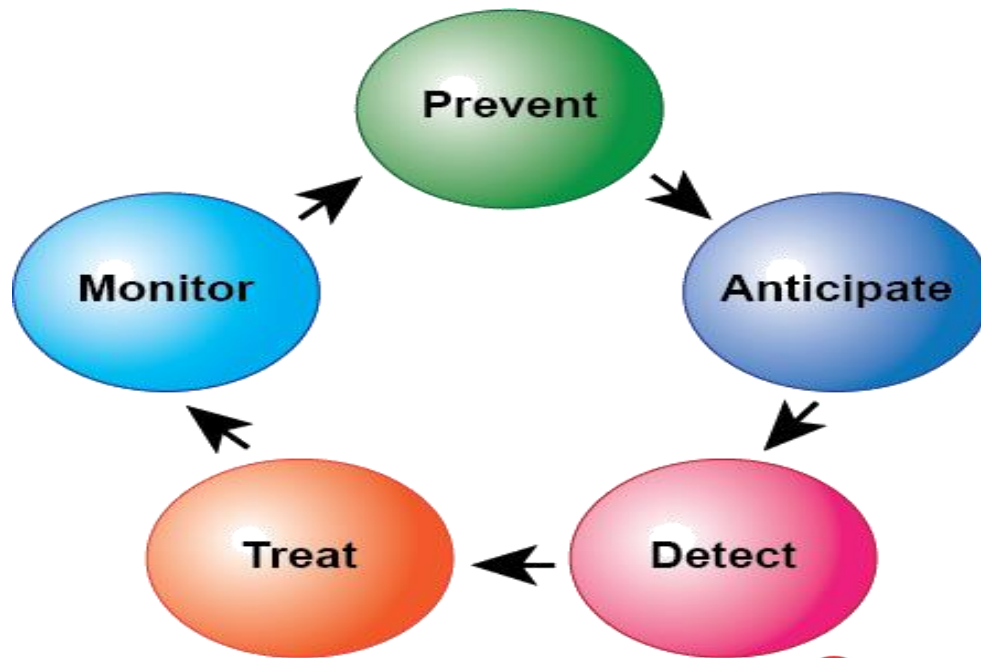
## Case Study



- Mr. M.C. is a 65-year-old male with a recent diagnosis of stage IV melanoma to the lungs. Patient has consented to start pembrolizumab (checkpoint inhibitor) at 2mg/kg every 3 wks.
- Mr. M.C and family would like to know what are the most common adverse events with this immunotherapy?
- What is the nurse's role in managing these toxicities?



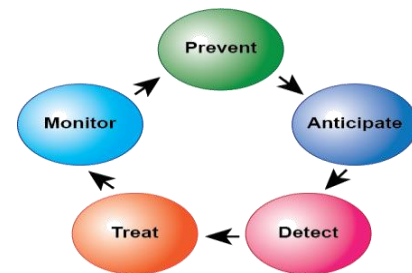
# The Five Pillars of Toxicity Management





# Nurse's Role in Management of Patient's Receiving Immunotherapy

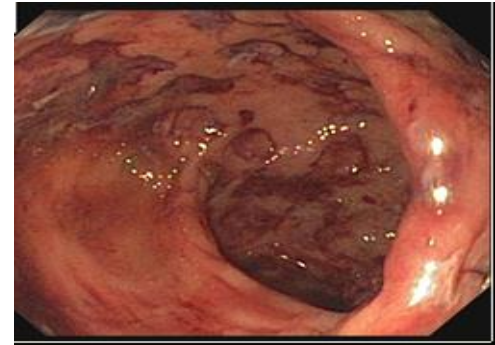
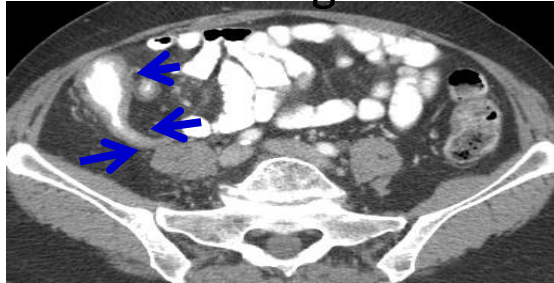
- Review & assess
  - Co-morbidities (dermatologic, endocrinopathies, gastrointestinal)
  - Medications
- Patient & family education
  - Most common side effects, including variability in the timing of onset
  - Importance of early & ongoing communication regarding side effects
  - Most common treatment of these toxicities





# irAEs and Autoimmunity

irAEs from CPI therapies result from immune dysregulation targeting normal tissue antigens.



Images courtesy of Dr.  
Adi Diab



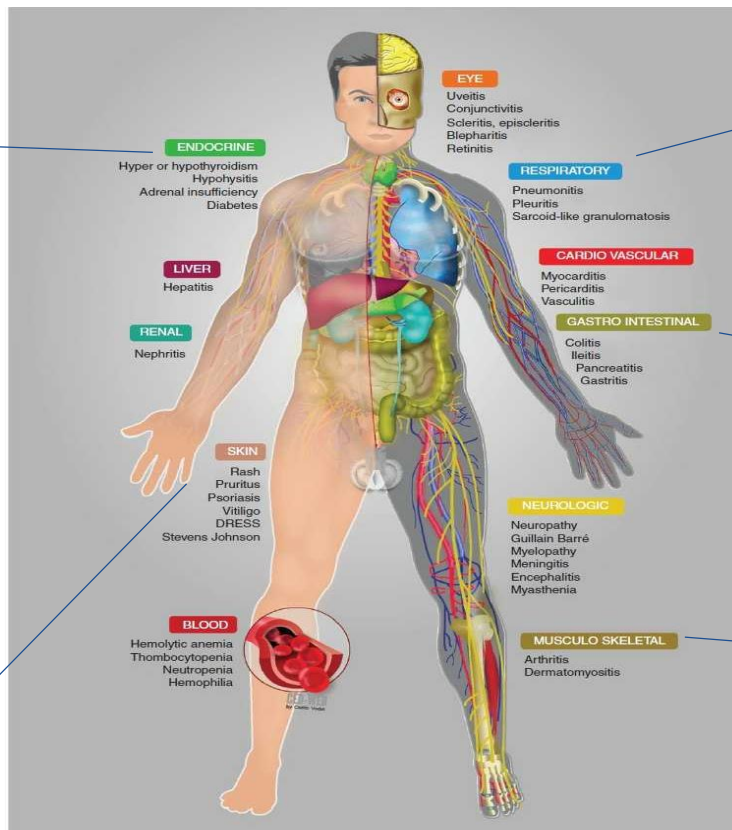


# Toxicity Spectrum: Immune Related Adverse Events

**Hypothyroid**  
**Hypophysitis**  
**Adrenal insufficiency**  
**Diabetes**

**Maculopapular rash**  
**Pruritus**  
**DRESS**  
**Vitiligo (positive factor)**

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**Shortness of breath**  
**Dyspnea on exertion**  
**Cough**

**Colitis**  
**Pancreatitis**

**Arthritis**





# Symptoms to look for with immune check-point inhibitors

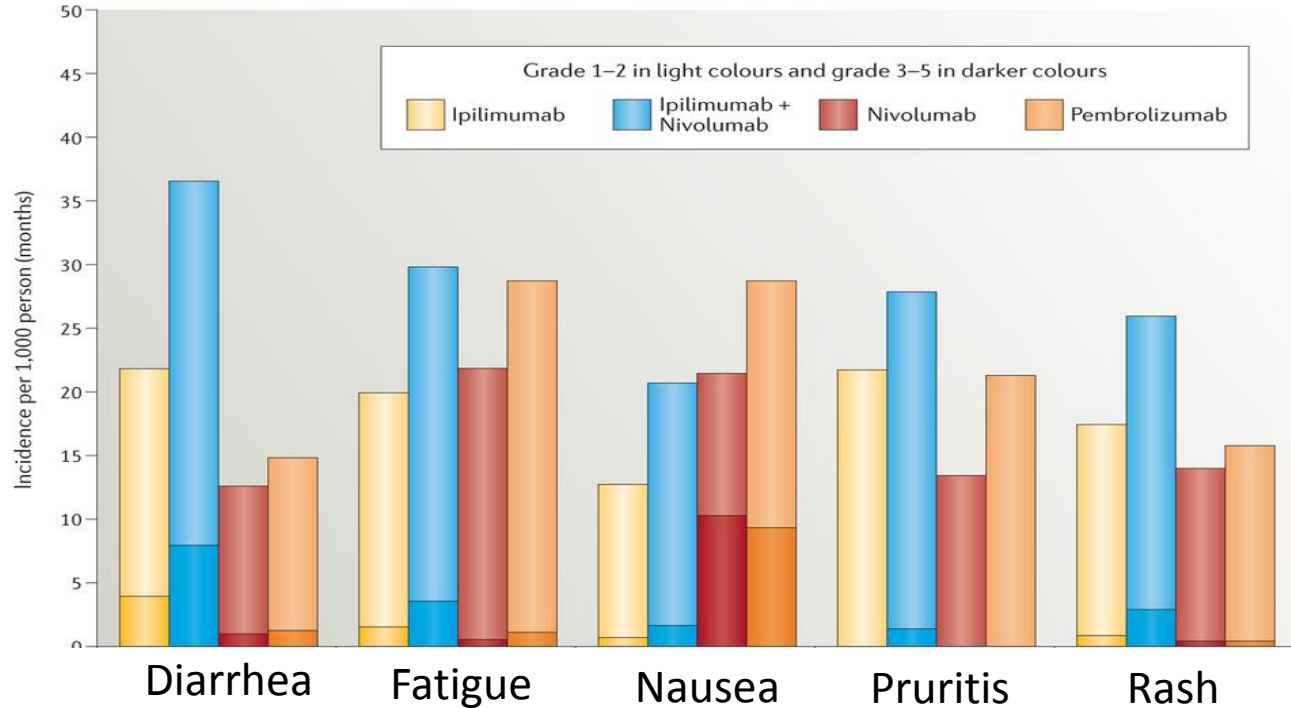
**Ipilumamab:**



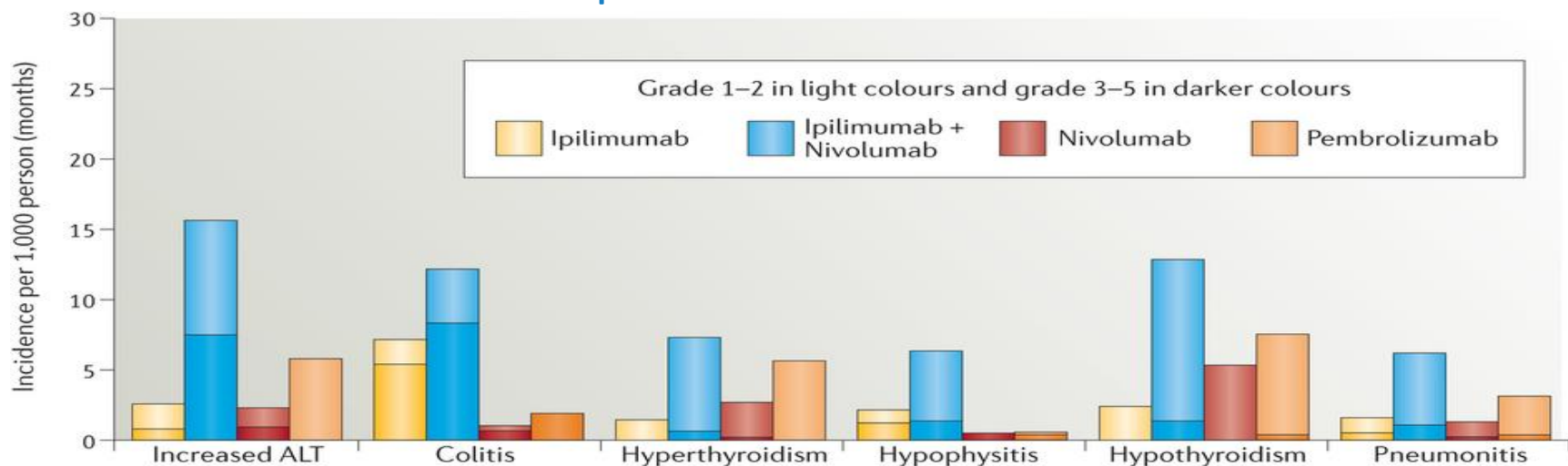
**Nivolumab:**



**Pembrolizumab:**



# Clinical features for adverse events with immune check-point inhibitors

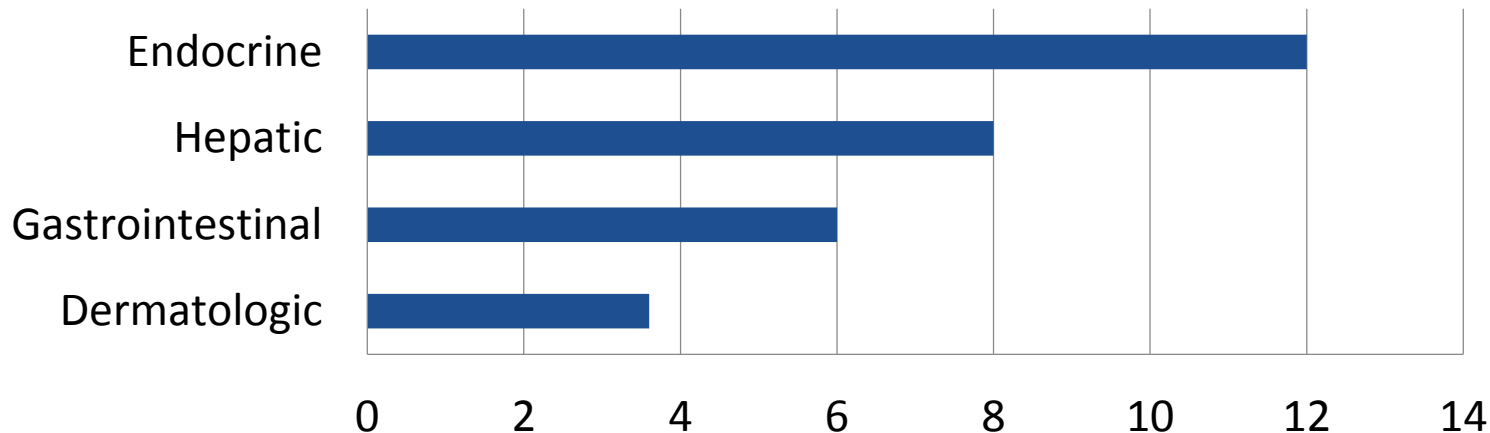


Nature Reviews | Clinical Oncology



## Immune checkpoint inhibitors-irAEs

### Median time to development (weeks)



# Educate patients: constant communication of symptoms is essential sooner rather than later

- Updated safety information with 9 additional months of follow-up were consistent with the initial report

Patients reporting event, %	NIVO+IPI (N=313)		NIVO (N=313)		IPI (N=311)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Treatment-related adverse event (AE)	95.8	56.5	84.0	19.8	85.9	27.0
Treatment-related AE leading to discontinuation	38.7	30.7	10.5	7.3	15.4	13.5
Treatment-related death*	0		0.3		0.3	

- 68.8% of patients who discontinued NIVO+IPI due to treatment-related AEs achieved a response

\*One reported in the NIVO group (neutropenia) and one in the IPI group (colon perforation)

Database lock Nov 2015

12

# Educate patients: constant communication of symptoms is essential sooner rather than later

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	NIVO+IPI (N=313)		NIVO (N=313)		IPI (N=311)	
Patients reporting event, %	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4

**Grade 3/4 is life-threatening**

Treatment-related death*	0		0.3		0.3	
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- 68.8% of patients who discontinued NIVO+IPI due to treatment-related AEs achieved a response

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# Managing irAEs

**Table 4.** Typical management of irAEs

Severity— CTCAE grade	Ambulatory versus inpatient care	Corticosteroids	Other immunosuppressive drugs	Immunotherapy
1	Ambulatory	Not recommended	Not recommended	Continue
2	Ambulatory	Topical steroids or Systemic steroids oral 0.5–1 mg/kg/day	Not recommended	Suspend temporarily <sup>a</sup>
3	Hospitalization	Systemic steroids Oral or i.v. 1–2 mg/kg/day for 3 days then reduce to 1 mg/kg/day	To be considered for patients with unresolved symptoms after 3–5 days of steroid course Organ Specialist referral advised	Suspend and discuss resumption based on risk/benefit ratio with patient
4	Hospitalization consider intensive care unit	Systemic steroids i.v. methylprednisolone 1–2 mg/kg/day for 3 days then reduce to 1 mg/kg/day	To be considered for patients with unresolved symptoms after 3–5 days of steroid course Organ specialist referral advised	Discontinue permanently

CTCAE = Common Terminology Criteria for  
Adverse Events

Champiat S, et al, Ann Oncol, 2016



# General Principles of Toxicity Management

- Reversible toxicities when recognized quickly and treated appropriately
- Treatment may include:
  - Corticosteroids (initiate at 1 -2 mg/kg/day of prednisone or equivalent)
  - Consider other therapies if no improvement with corticosteroids; such as tumor necrosis alfa (TNF- $\alpha$ ) antagonists (infliximab) for GI toxicities and mycophenolate mofetil in hepatotoxicity.
  - Dose delay, omission or discontinuation of the immunotherapy; should hold immunotherapy for grade  $\geq 2$
- Corticosteroids may require a long tapering duration to prevent recurrence of symptoms
- Re-challenge with checkpoint inhibitor may only be done, if clinically appropriate, once a patient is receiving 10 mg of oral prednisone or equivalent or less.







## Case Study - rash

Mr. M.C. returns to clinic for evaluation prior to dose #4 of pembrolizumab.



He reports that for the past week he has had a pruritic rash on his chest, abdomen and arms.

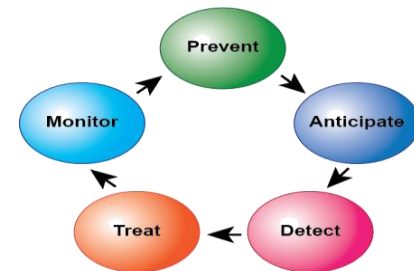
# Nurse's role: rash

## Anticipate/Prevent

- Skin toxicities can be seen in up to 58% of cases
- Autoimmune conditions can worsen
- Occupational/recreational activities (exposure to outdoors/high temps can worsen skin AEs)
- Possibility of developing hypopigmentation (vitiligo correlated to positive outcome)

## Monitor

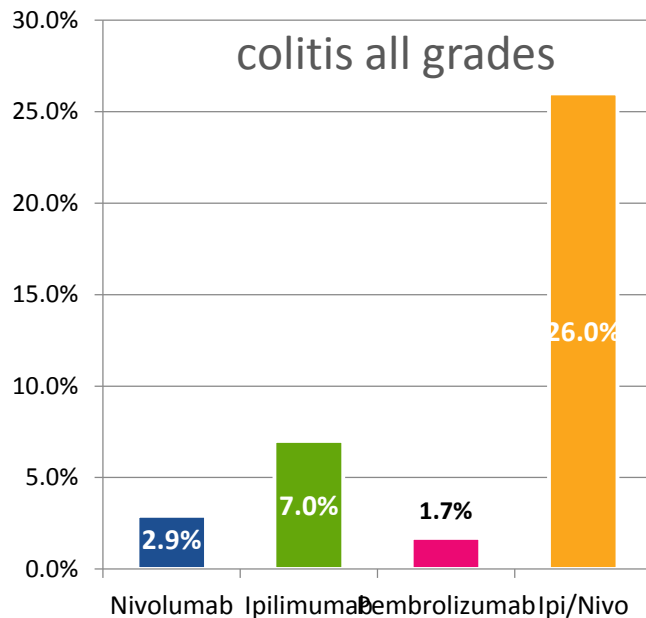
- New onset of rash
- New lesions
- Itching
- Sunburn
- Photosensitivity



## Manage

- Educate patient about potential side effects
- Grade 1: topical OTC hydrocortisone / oral diphenhydramine
- Grade 1/2: triamcinolone or clobetasol cream, diphenhydramine or hydroxyzine (if and when)
- Grade 2: hold treatment, oral corticosteroids
- Grade 3/4: discontinue agent

# Immune-Mediated Colitis



BMS PI, 2017

MERK PI, 2017

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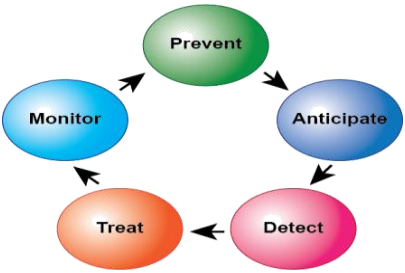
## Nurse's role: GI toxicities

### Anticipate/Prevent

- Diarrhea can be seen in up to 48% of cases
- Autoimmune conditions can worsen
- Avoid foods that cause loose stools
- Rule out infections (c-diff)
- Remain well-hydrated

### Monitor

- Worsening loose stools
- Dehydration
- Abdominal pain/cramping
- Bloody stools



### Manage

- Educate patient about potential side effects
- Grade 1: hydration, loperamide, bland diet
- Grade 2: diphenoxylate/atropine QID, budesonide, stool studies, possible sigmoidoscopy/colonoscopy & steroid taper
- Grade 3/4: discontinue agent, IV steroids and fluids (if not effective, infliximab)



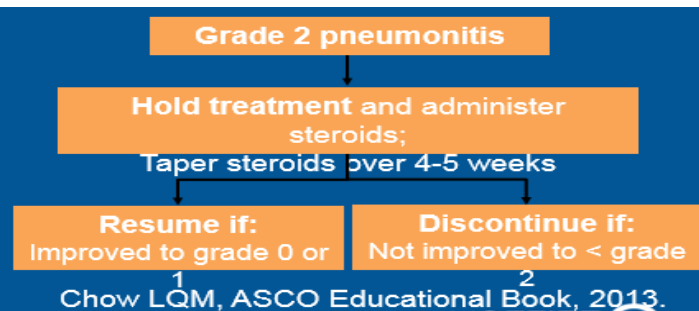
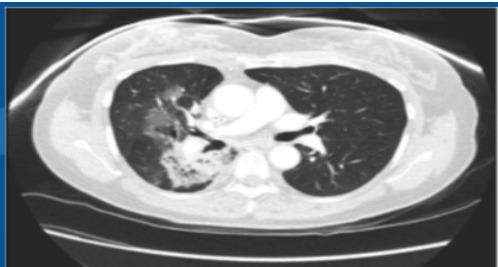
## Case study

- B.C. is 56-year-old female with a diagnosis of Stage IV melanoma. She is now on nivolumab 240 mg every two weeks infused over 60 minutes. Today she reports that for the past five days she has had SOB, cough and DOE.
- O<sup>2</sup> saturations at RA 95% and 89% during ambulation
- As the primary nurse, what would be your best course of action?

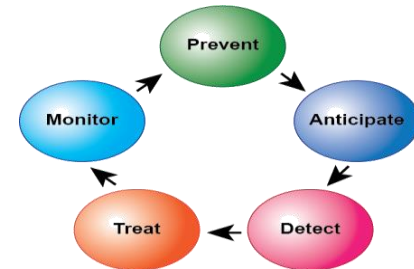


# Pneumonitis is more common with anti-PD1/CTLA-4 combination therapy

- Important to address respiratory symptoms and check oxygen saturations at each visit
- On any patients where pneumonitis is suspected based on H&P or clinical exam, provider will hold treatment and order a CT scan of the chest.
- Specific management is necessary for grade 2 or greater pneumonitis.



# Nurse's role: pneumonitis



## Anticipate/Prevent

- Pneumonitis on single vs combination immunotherapy
- Exposure to heavy smoke areas / smoking cessation
- Vaccinations (flu + pneumonia)
- Pneumonia vs PE vs CHF

## Monitor

- SOB, DOE, CP, persistent cough, fevers, worsening fatigue
- Pulse-ox at rest and ambulation

## Manage

- Educate patient about potential side effects
- Grade 1: asymptomatic
- Grade 2: chest x-ray or CT, anticipate steroid taper
- Grade 3/4: discontinue agent, IV steroids and fluids (if not effective, infliximab), oxygen therapy



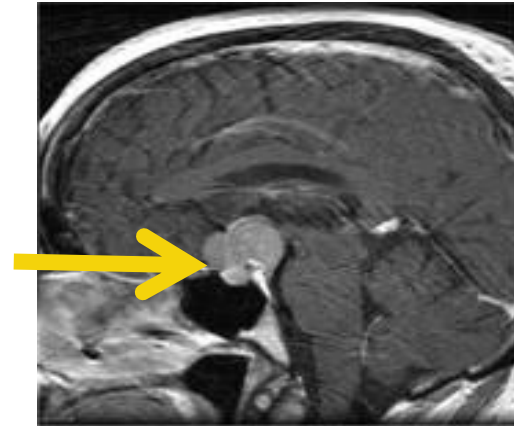
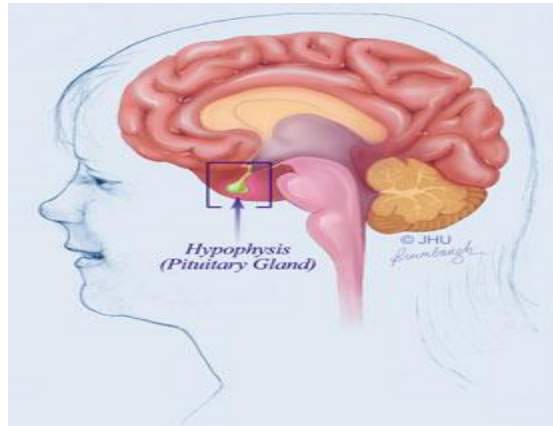
## Case study

- J.C. is a 75-year-old male with metastatic melanoma currently on nivolumab/ipilimumab combination therapy. He reports that for the past five days he has had:
  - Moderate headaches, severe fatigue, weakness and nausea.
  - Endocrine labs revealing low cortisol, low ACTH and low testosterone levels. Free T4 and TSH were normal.
- As the nurse you see the patient first in clinic and alert the doctor of his symptoms and current labs.



## Case study

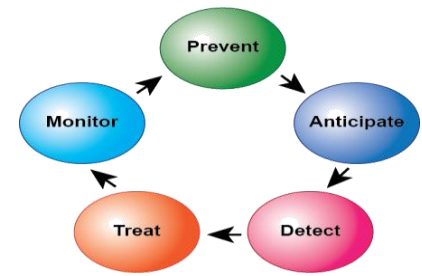
Oncologist orders an MRI of the brain which shows inflammation of the pituitary gland



# Immune-mediated endocrinopathies

- More common with anti-PD-1 than anti CTLA-4
- Hypophysitis - with nivo/ipi median time to onset was about 2.7 months. All grades 9%
- Hypothyroidism
- Hyperthyroidism
- Adrenal insufficiency
  - Rule out brain metastasis
  - Hold for symptoms and/or any Grade 3/4
  - Give steroids (IV followed by PO 1-2mg/kg) tapered over four weeks and replace appropriate hormones
    - Hormone replacement may be required for life in ~50% of patients

# Nurse's role: endocrinopathies



## Anticipate/Prevent

- Hypothyroidism
- Hyperthyroidism
- Hypophysitis
- Adrenal insufficiency
- Especially in combination ipi/nivo

## Monitor

- Labs: Free T4, TSH, ACTH, cortisol and testosterone (in males)
- Worsening fatigue
- Constipation
- Headaches
- Dizzy episode(s)
- Muscle weakness

## Manage

- Hormonal replacement therapy or steroid taper accordingly

# Immune checkpoint inhibitors irAEs

- Rare toxicities
  - Type I and II diabetes mellitus
  - Pancreatitis-usually asymptomatic amylase/lipase elevations (hold for grade 3/4)
  - Myositis
  - Renal toxicity (acute interstitial nephritis)
  - Autoimmune myocarditis
  - Neurologic toxicities



# Immune checkpoint inhibitors irAEs

Rare toxicities

Bullous pemphigoid



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- Bullous pemphigoid
- Myasthenia-like syndrome-motor paralysis, intravenous immune globulins
- Optic neuritis-photophobia, pain, blurred vision, may correlate with colitis
- Sarcoidosis-lymphadenopathy
- Hematologic toxicities

## Case Study

JW is a 37 yo female with Stage IV M1c metastatic melanoma with metastases to multiple lymph nodes and left femoral head.

- She was seen as a new patient for treatment options; she was treatment naïve.
- She was consented to begin treatment on ipilimumab + nivolumab on protocol.



## Case Study

- 3/5, she received dose #1 of both drugs
- 3/10, seen in clinic for low back pain; she was initiated on antibiotics for UTI.
- 3/12, the pain persisted and she underwent CT abdomen and pelvis.
- 3/12, shortly thereafter she began having high fever with chills and subsequently went to the emergency center with fevers, chills, headaches and overall malaise.

## Case Study

### Hospital Course:

- Complete infectious work-up performed including respiratory panel, urine and blood cultures (all negative).
- CXR unremarkable.
- Initiated on Cefepime and Vancomycin.
- She continued to have fevers up to 39.6.
- MRI brain and Endocrine work-up unremarkable; no evidence of hypophysitis.

## Case Study

- After admission she began experiencing a dry cough. Baseline CXR unremarkable.
- 3/17, she was noted to have change in respiratory status with mild hypoxia, worsening cough and tachycardia.
- She was given anti-tussives and nebulizers and repeat CXR performed.
- Because of abnormalities on CXR, CT chest performed and pulmonary consulted.
- Her respiratory status declined quickly and by the time the CT performed she was on 4 L of oxygen.



CXR  
3/13



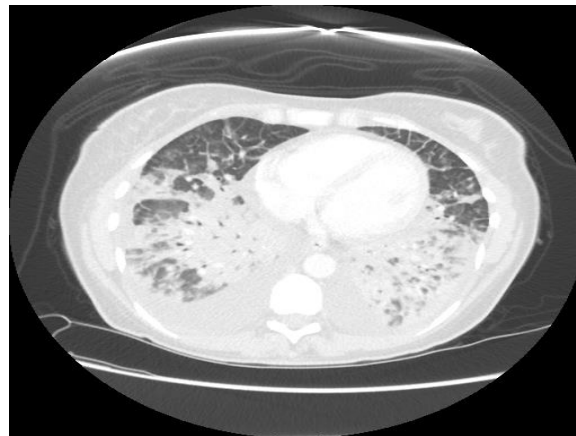
CXR  
3/17



CT  
3/12



CT  
3/17



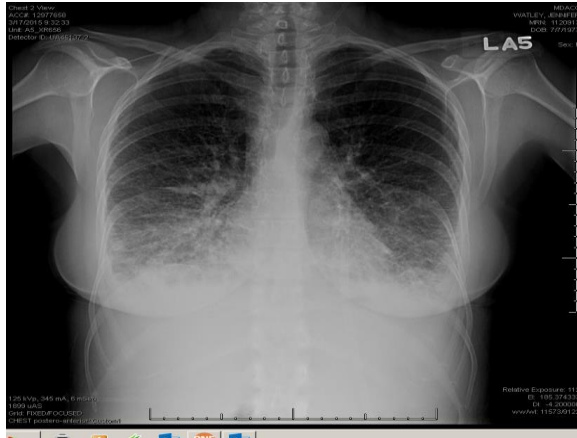
## Case Study

- ICU team was notified of potential transfer to ICU due to acutely worsening respiratory status.
- She was initiated on methylprednisolone, 2mg/kg/day.
- Two hours after initiating steroids, she had overwhelming improvement in her symptoms.
- By the following day she had resolution of headaches, tachycardia and was weaned completely off of the oxygen in less than 2 days.
- In addition, she began experiencing severe diarrhea and transaminitis. These symptoms also resolved with the addition of the steroids.
- She was discharged on a prednisone taper 8 days after admission.



## Case Study

CXR 3/17



CXR 3/19



## Conclusions

- Nurses have an ESSENTIAL role in monitoring and managing patients undergoing treatment with immunotherapy.
- Potential irAEs grade 2 and above require frequent visits, drug hold/discontinuation and corticosteroids.
- Combination anti-PD-1/CTLA-4 immunotherapy significantly increases the grade 3-4 AE rate.
- Close monitoring for irAEs is mandatory for prevention of serious adverse events, decreased ER visits and improved patient outcomes.
- As immunotherapies indications broaden, our understanding of toxicity identification and management is essential to make the risk-benefit ratio favorable.