ADVANCES IN Cancer IMMUNOTHERAPY™

Nursing Perspective on irAEs: Patient Education, Monitoring and Management

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Association of Community Cancer Centers

Society for Immunotherapy of Cancer

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Disclosures

- Not available at time of printing.
- I *will not* be discussing non-FDA approved indications during my presentation.

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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

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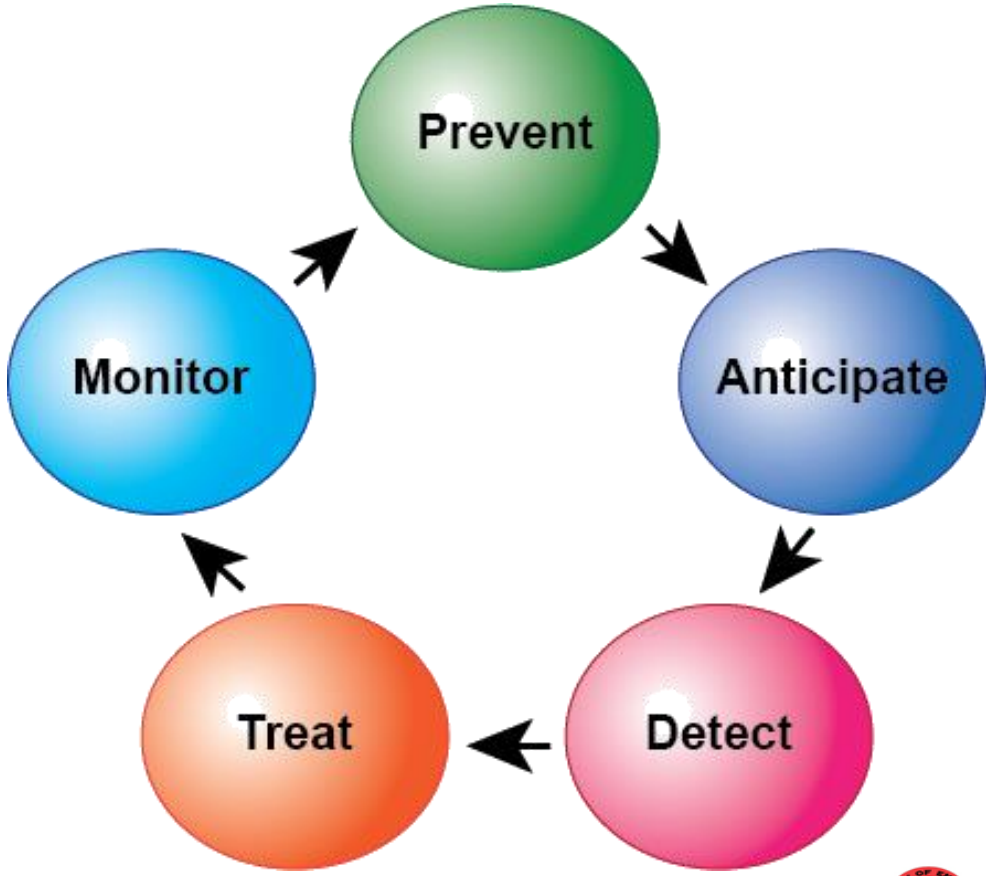
The Five Pillars of Toxicity Management



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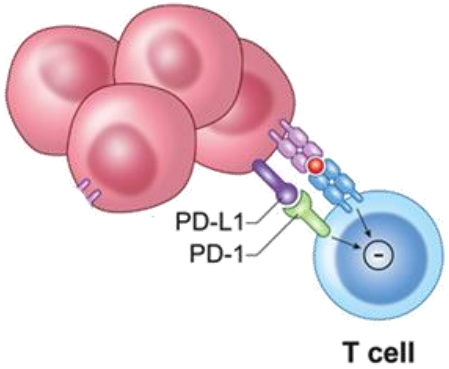
Case Study



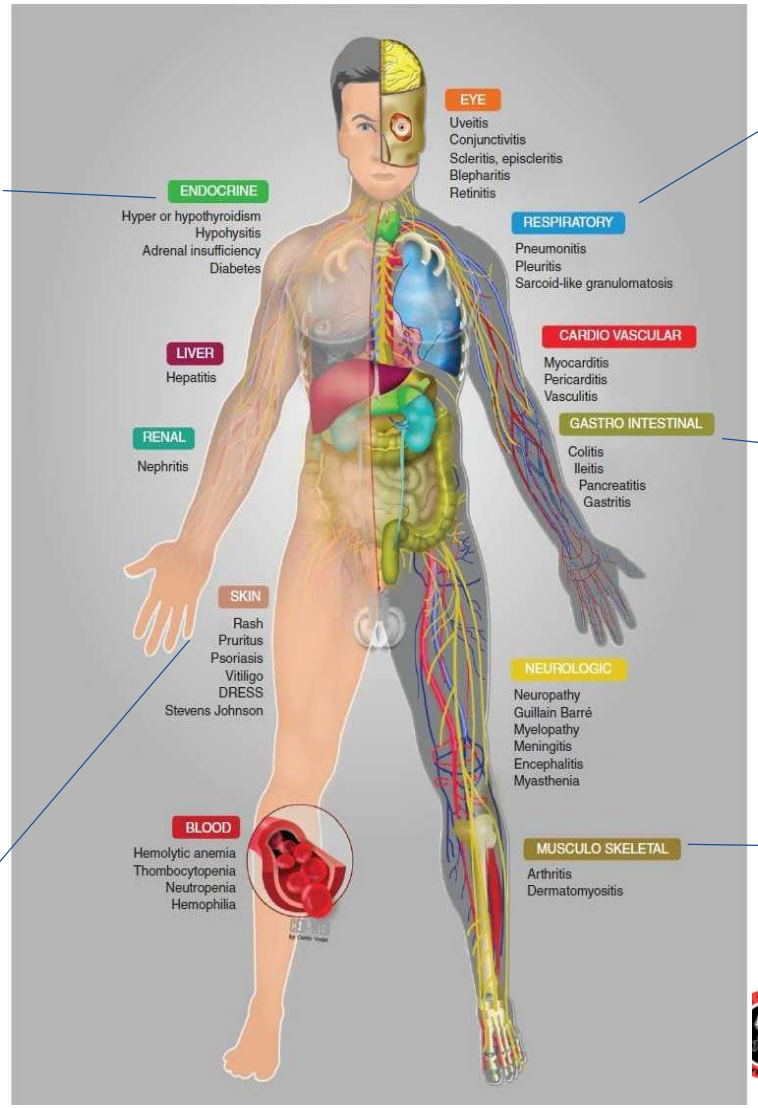
- Mr. M.C. is a 65-year-old male with a recent diagnosis of stage IV melanoma to the lungs. Patient has consented to start pembrolizumab (checkpoint inhibitor) at 2mg/kg every 3 wks.

- Mr. M.C and family would like to know what are the most common adverse events with this immunotherapy?

Toxicity Spectrum: Immune Related Adverse Events

Hypothyroid
Hypophysitis
Adrenal insufficiency
Diabetes

Maculopapular rash
Pruritus
DRESS
Vitiligo (positive factor)



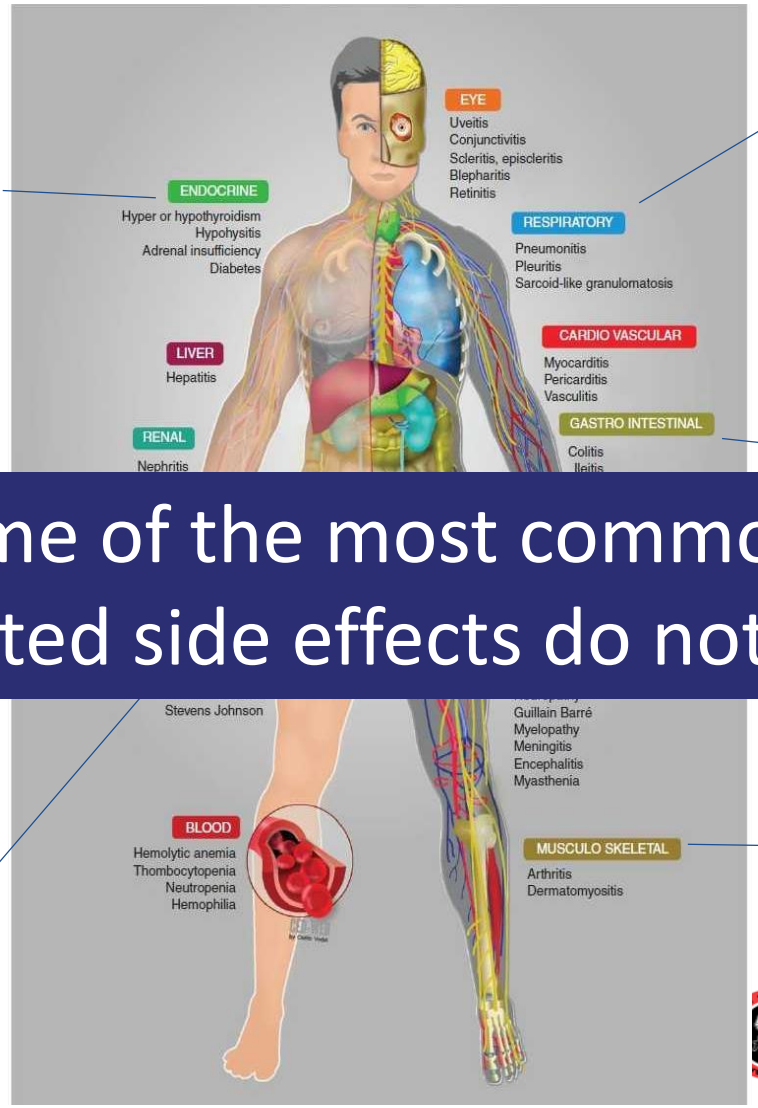
Shortness of breath
Dyspnea on exertion
Cough

Colitis
Pancreatitis

Arthritis

Toxicity Spectrum: Immune Related Adverse Events

Hypothyroid
Hypophysitis
Adrenal insufficiency
Diabetes



Shortness of breath
Dyspnea on exertion
Cough

Colitis

These are some of the most common; HOWEVER; immune-related side effects do not discriminate.

Maculopapular rash
Pruritus
DRESS
Vitiligo (positive factor)

Arthritis

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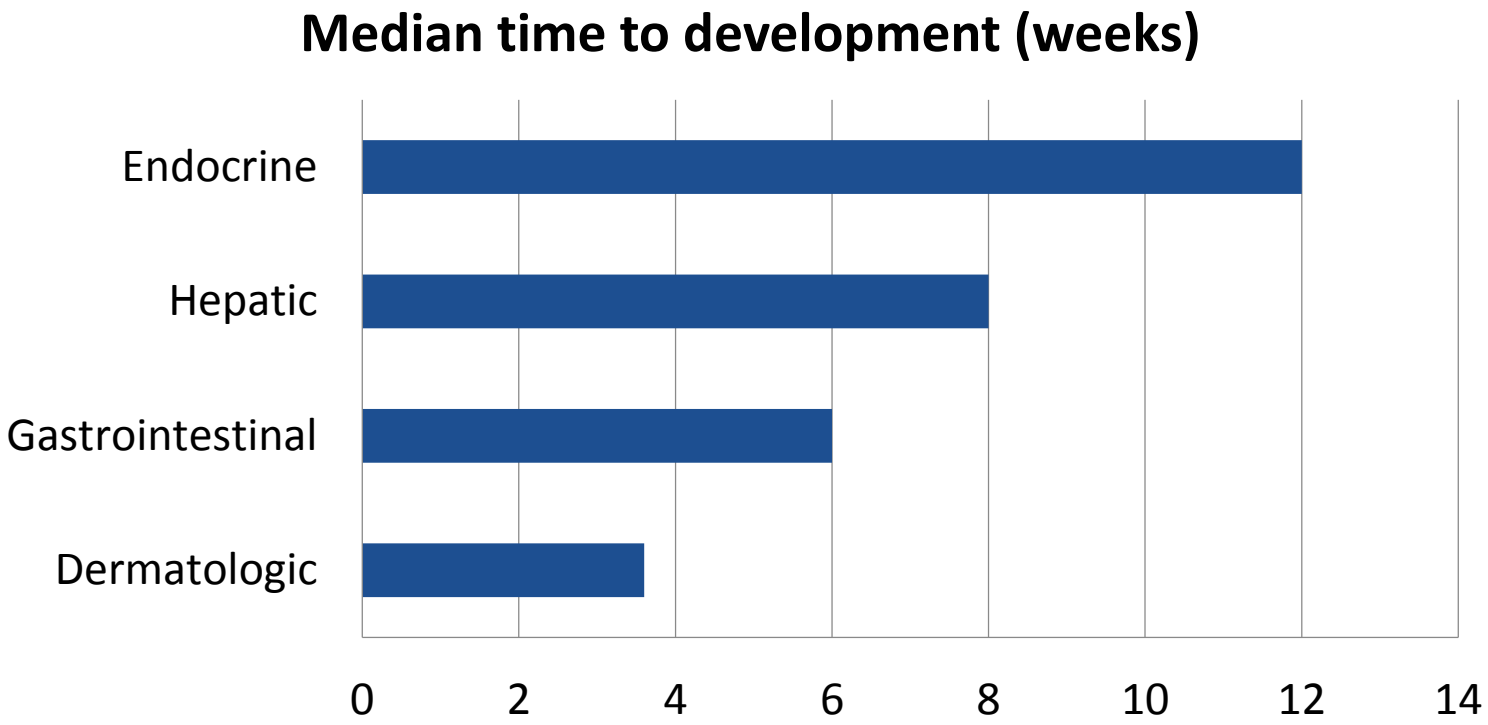
Immune checkpoint inhibitors-irAEs



Weber J et al, J clin Oncol 2012

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Symptoms to look for with immune check-point inhibitors

Ipilumamab:

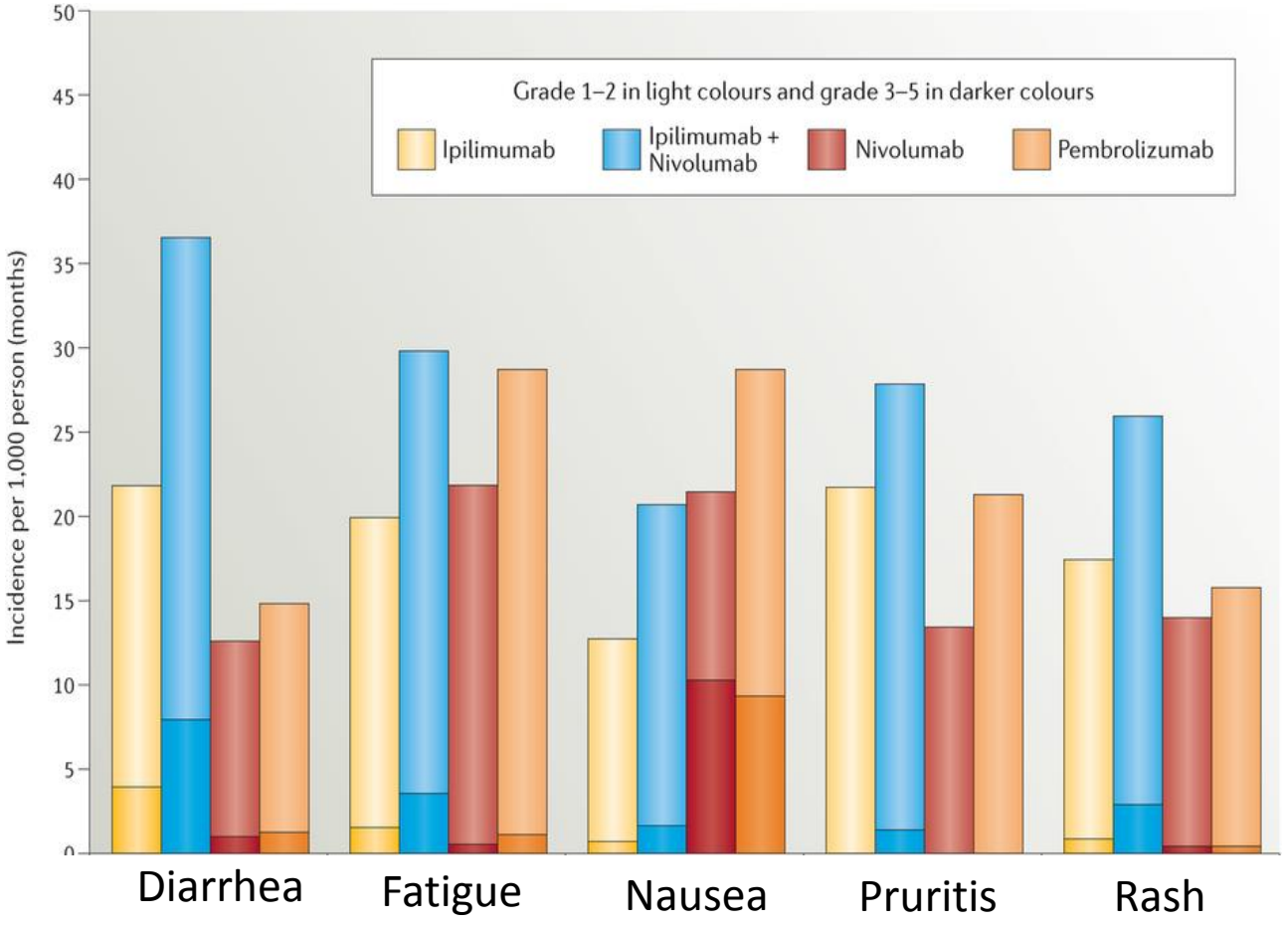
CTLA-4

Nivolumab:

PD-1

Pembrolizumab:

PD-1



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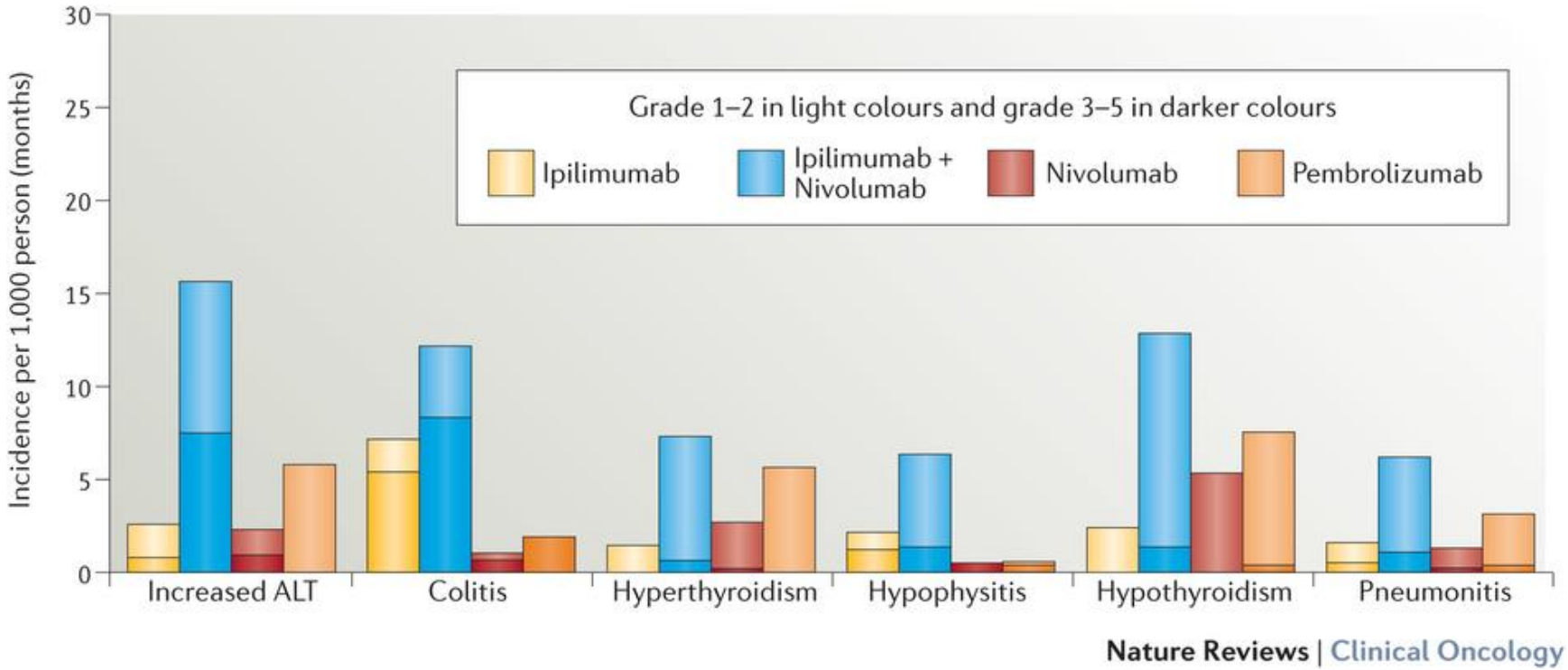
Clinical features for adverse events with immune check-point inhibitors



Nature Reviews | Clinical Oncology

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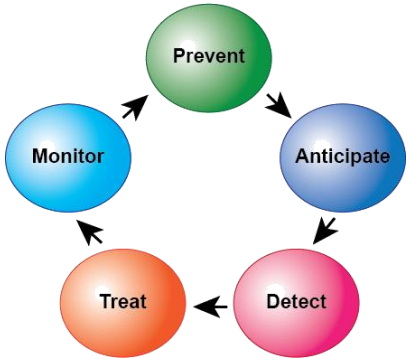

Nurse's Role: Prior to Immunotherapy

- 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
  - Appropriate skin care during immunotherapy treatment, initiate now

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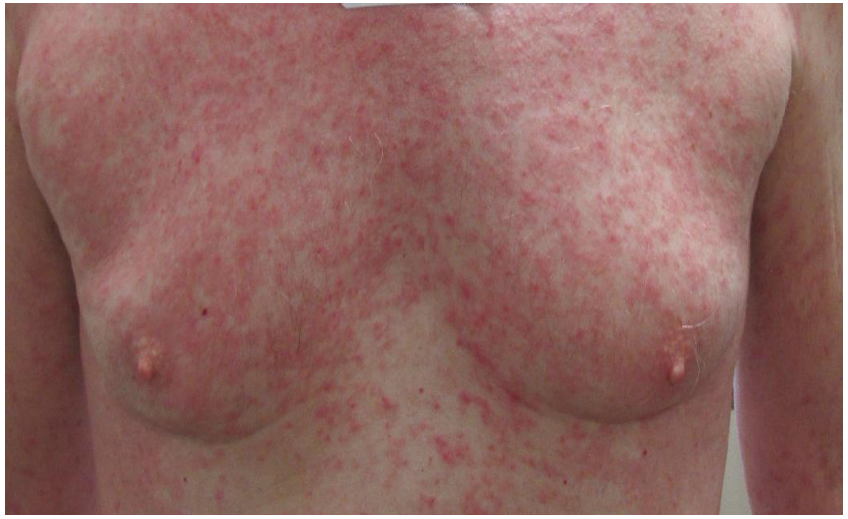
Case Study - rash

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.

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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[a]
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

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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				
2				
3				ion based atient
4				

Principles of Managing irAEs:

- **Hold immunotherapy for grade ≥ 2**
- **Initiate corticosteroids (e.g.,1–2 mg/kg of prednisone)**
- **Consider other therapies (example: infliximab if gastrointestinal toxicity or mycophenolate if hepatotoxicity, if no improvement with corticosteroids)**

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Champiat S, et al, Ann Oncol, 2016

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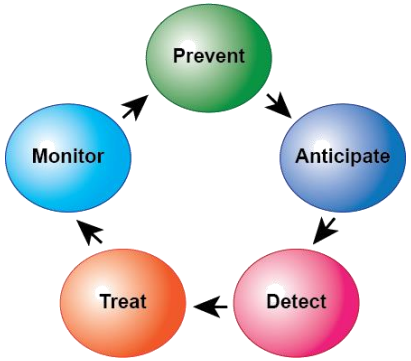
Nurse's role: rash



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

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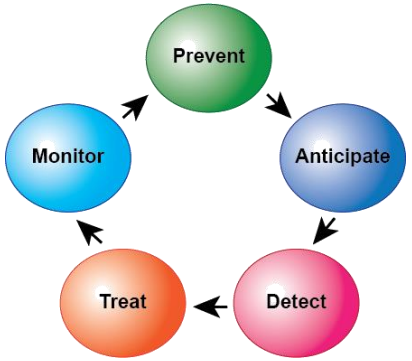
Nurse's role: rash



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MOST IMPORTANT:
CONTACT HEALTH CARE PROVIDERS IMMEDIATELY!! COME IN NOW!!!

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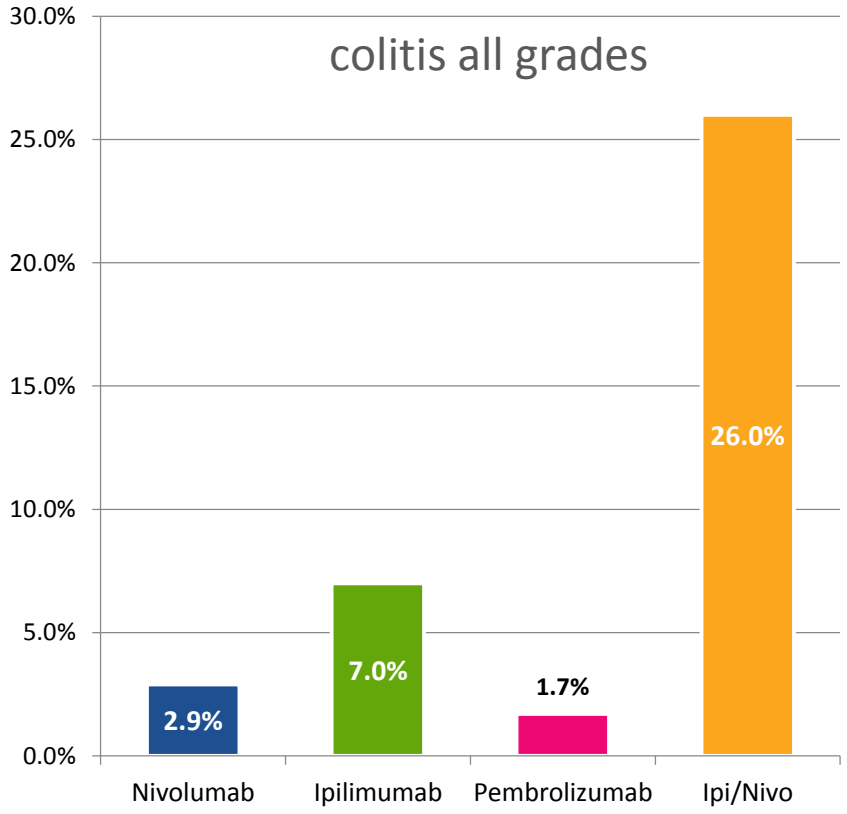
Immune-Mediated Colitis



BMS PI, 2017
MERK PI, 2017

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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

	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
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

Larkin J et al, N Engl J Med, 2015
Wolchock J, et al ASCO, 2016

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Grade 3/4 is life-threatening

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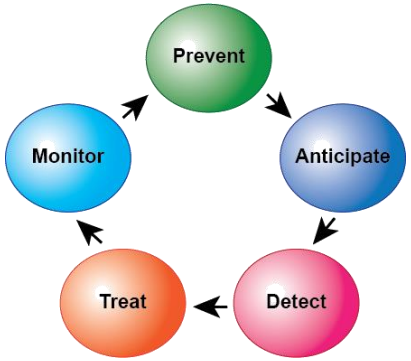

Nurse's role: GI toxicities

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)

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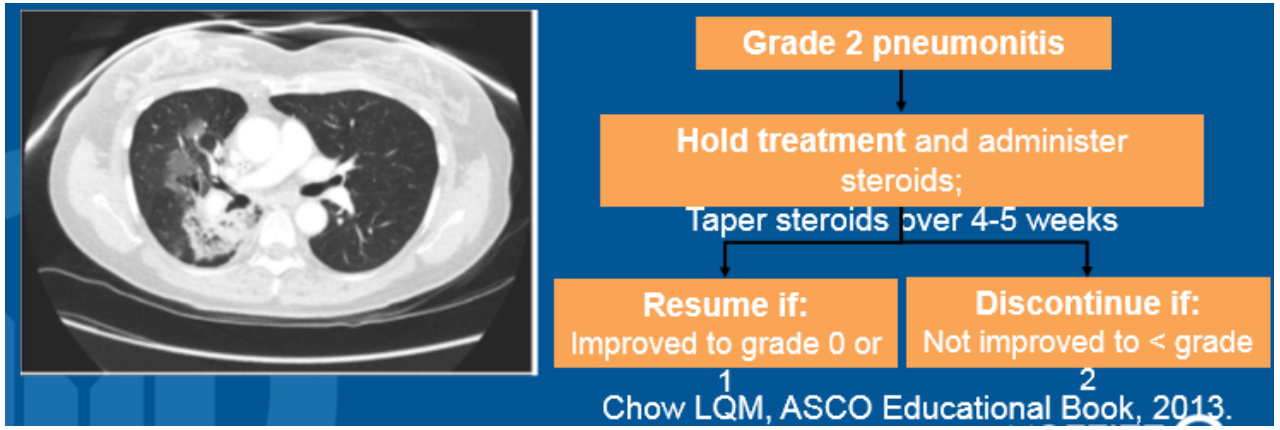
Case study

- 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^2 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.



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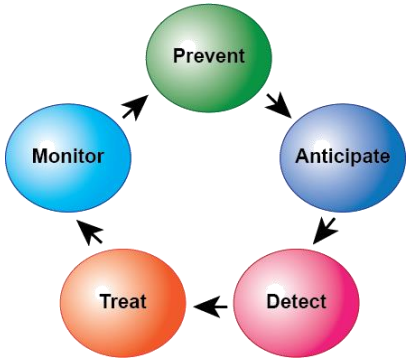

Nurse's role: pneumonitis

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

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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.

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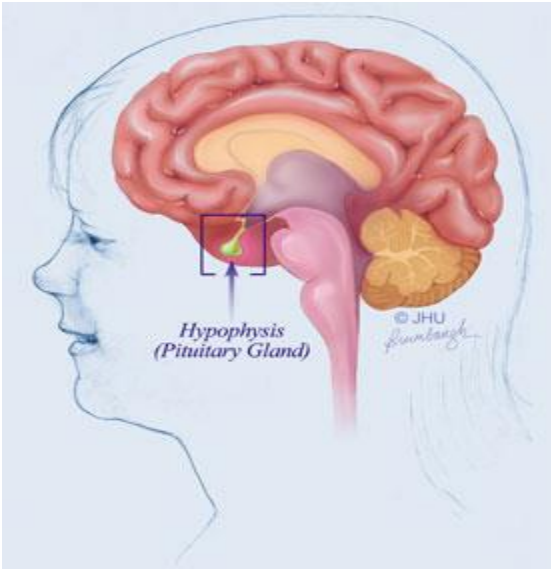
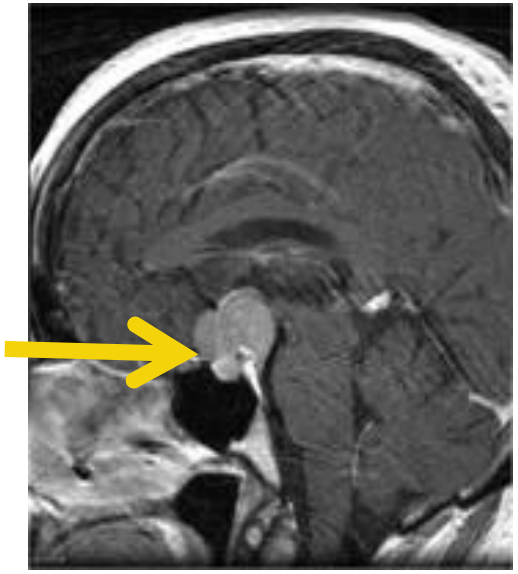
Case study

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





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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

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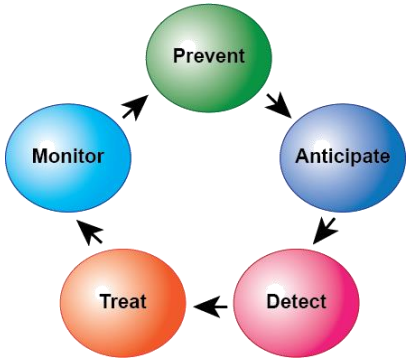

Nurse's role: endocrinopathies

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

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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
  - Bullous pemphigoid

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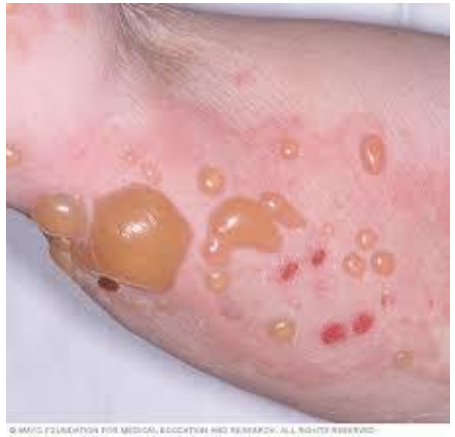
Immune checkpoint inhibitors irAEs

Rare toxicities

Bullous pemphigoid



- Myasthenia-like syndrome-motor paralysis, intravenous immune globulins
- Optic neuritis-photophobia, pain, blurred vision, may correlate with colitis
- Sarcoidosis-lymphadenopathy, increased angiotensin converting-enzyme level, biopsy is granulomata, PET positive
- Hematologic
- Cardiotoxicities: Myocarditis

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Immune-mediated toxicities

- General principles of toxicity management
  - Reversible toxicities when recognized quickly and treated appropriately
  - Treatment may include dose delay, omission, or discontinuation, corticosteroids, tumor necrosis alfa (TNF-α) antagonists, and mycophenolate mofetil
  - Corticosteroids may require a long tapering duration to prevent recurrence of symptoms
    - Rechallenge with checkpoint inhibitor may only be done, if clinically appropriate, once a patient is receiving 10 mg of oral prednisone or equivalent or less.
    - Prolonged use of steroids predisposes patients to systemic infection so prophylaxis may be indicated.

Villadolid J and Amin A. *Transl Lung Cancer Res* 2015; 4 (5): 560-575

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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.

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