Management of Adverse Events From Cancer Immunotherapy

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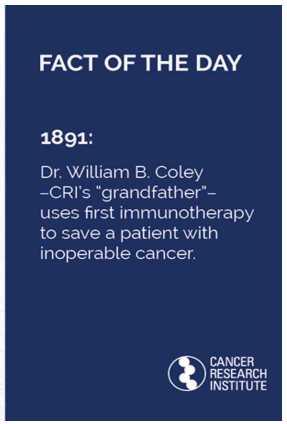
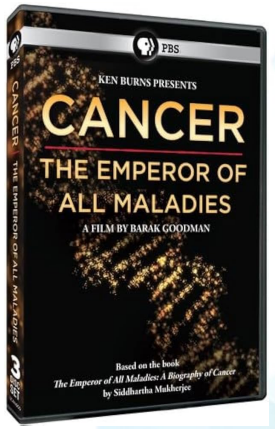
Clinical oncologist

History of Immunotherapy

- William Coley (January 12, 1862 – April 16, 1936)
- Injecting patients with a mixture of heat-killed bacteria in the hopes of stimulating the body's "resisting powers
- Coley's approach was abandoned because other doctors could not replicate his results





- Number of patients treated with ICIs is rapidly growing
- ICIs now approved as monotherapy, in combination with other ICIs, and in combination with chemotherapy
- ICIs historically used in later-line metastatic disease
- Moving into earlier lines of therapy and earlier stages of disease (eg, adjuvant tx for melanoma; tx for stage III NSCLC)
- Patients may receive ICI therapy for years, as optimal duration is unknown

Immunotherapy indications

Immunotherapy vs Chemotherapy

• Majority without	• Almost all patients
• Variable	• Well described
• Any organs	• Few organs
• Variable	• Well established

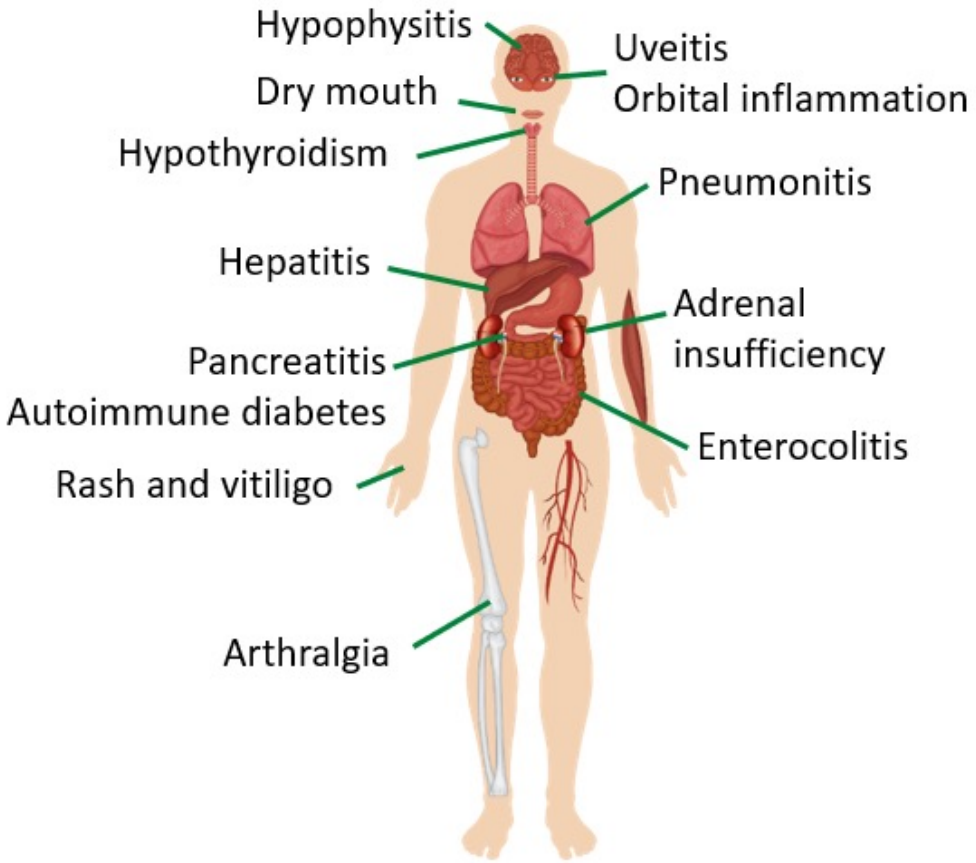
Immune-Related AEs

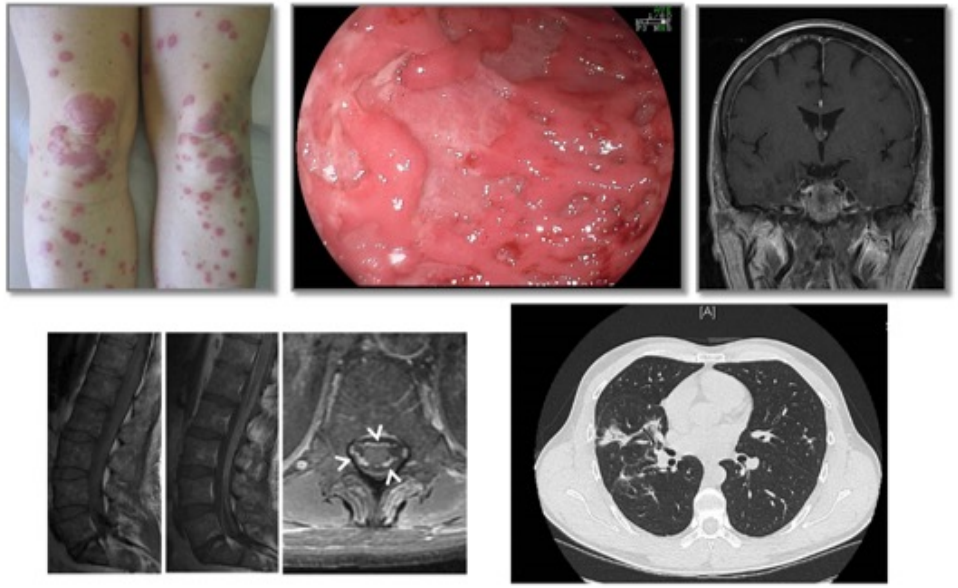
- ICIs introduce the potential for transformative, durable responses in multiple malignancies
- ICIs also introduce the potential for new toxicity
- Immune-related AEs
  - Activation of immune cells in nontumor compartments
  - Can mimic **autoimmune conditions**

Immune-Related AEs

- 1 in 10 get G3 or G4 toxicity (better than chemo)
- 1 in 20 stop due to toxicity
- PD or PDL1 Ab monotherapy low incidence of any grade irAEs than with Anti- CTLA4
- Early occurrence within days to delayed onset up to 26 weeks

Immune-Related AEs Associated With ICIs





Understanding Immunotherapy Side Effects

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Immune checkpoint inhibitors (a type of immunotherapy) offer a promising new way to treat certain cancers. But these medicines can cause your immune system to attack normal organs and tissues in your body, affecting the way they work. Serious side effects typically occur in less than 5% of patients, but certain mild side effects can occur in up to 30% – 50% of patients.

Contact your health care provider right away if you think you may be experiencing ...

Pituitary gland
Low cortisol causing fatigue, loss of appetite, muscle weakness

Eyes
Blurred or distorted vision, blind spots, eye pain or redness, itchy or bulging eyes, new floaters

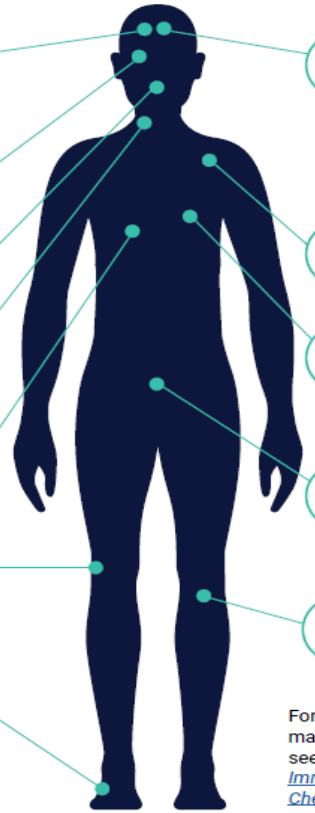
Mouth
Dry mouth, pain or burning, sores, changes in taste

Thyroid gland
Weight loss or gain, rapid heartbeat, fatigue, sweating, anxiety, constipation, dry skin, sensitivity to cold

Lungs
Shortness of breath, dry cough, chest pain, fever

Skin
Rash, itching, blisters, psoriasis, reddish-purple bumps and patches

Nerves
Numbness or tingling in hands or feet; unusual weakness in legs, arms, or face



Brain or spinal cord
Confusion, changes in behavior, headaches, seizures, short-term memory loss, problems speaking or reacting, sensitivity to light, neck stiffness, sensory problems, pain, fever, nausea or vomiting

Muscles
Muscle weakness, aches, pain, or stiffness

Heart
Fatigue, chest pain or pressure, irregular heartbeat, shortness of breath, swollen legs, ankles, or feet

Bowel
Watery stools, cramping, urgency, stomach-area pain, fever, blood or mucus in stool, nighttime bowel movements

Joints
Joint pain or swelling, stiffness after rest, improvement with activity

For other signs and symptoms that may occur with immunotherapy, please see the *NCCN Guidelines for Patients: Immunotherapy Side Effects – Immune Checkpoint Inhibitors*.

RED FLAG SYMPTOMS

Diarrhoea/colitis	Abdominal pain, bleeding, mucous, nocturnal diarrhoea
Hypophysitis	Headache, visual changes, extreme fatigue
Adrenal insufficiency	Low BP, dizzyness, fatigue, electrolyte disturbance
Thyroiditis	Tremor, diarrhoea, anxiety, palpitations, delirium
Pneumonitis	SOB, dry cough, check exertional sats if normal at rest
Neurological toxicity	Numbness, weakness, double vision, SOB, confusion, drowsiness, headache
Myocarditis	Chest pain
Rash	vesicles, blistering or mucous membrane involvement

Most Common irAEs in Patients With Cancer Presenting to Emergency Department

irAE, %	Ipilimumab (n = 186)	Nivolumab (n = 154)	Pembrolizumab (n = 109)	> 1 Agent (n = 179)
Diarrhea	14.5	8.4	6.4	18.4
Colitis	7.0	2.6	1.8	7.3
Pneumonitis	3.2	7.1	4.6	4.5
Dermatitis	4.3	4.5	4.6	7.8
Hypophysitis	4.3	0.6	0	5.0
Hepatitis	1.1	6.1	1.3	0.9
Thyroiditis	1.6	0.6	0	5.0
Pancreatitis	1.1	1.9	0.9	5.0
Adrenalitis	0.5	1.3	0	1.1

General Principles for Managing irAEs

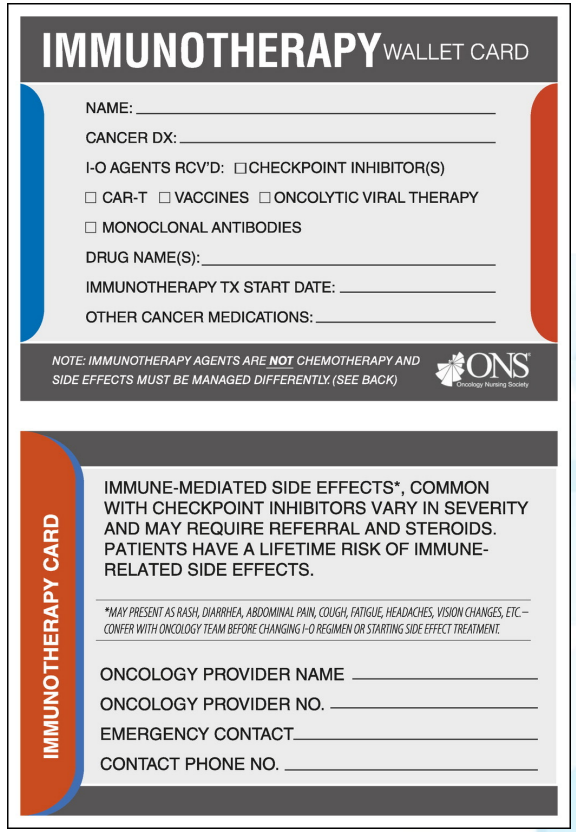
- Consult promptly with relevant specialists for affected organ systems (eg, gastroenterology, dermatology)
- Management generally based on severity of symptoms
  - **Mild (grade 1):** supportive care, consider holding drug
  - **Moderate (grade 2):** hold drug, redose if toxicity improves, consider low-dose steroids **(prednisone 0.5-1 mg/kg/day)**
  - **Severe (grade 3):** discontinue drug, monitor closely (likely inpatient), start high-dose steroids **(prednisone 1-2 mg/kg/day)** with a slow taper (≥ 1 mo)
    - If not improving in 1-3 days, increase immunosuppression

General Principles for Managing irAEs

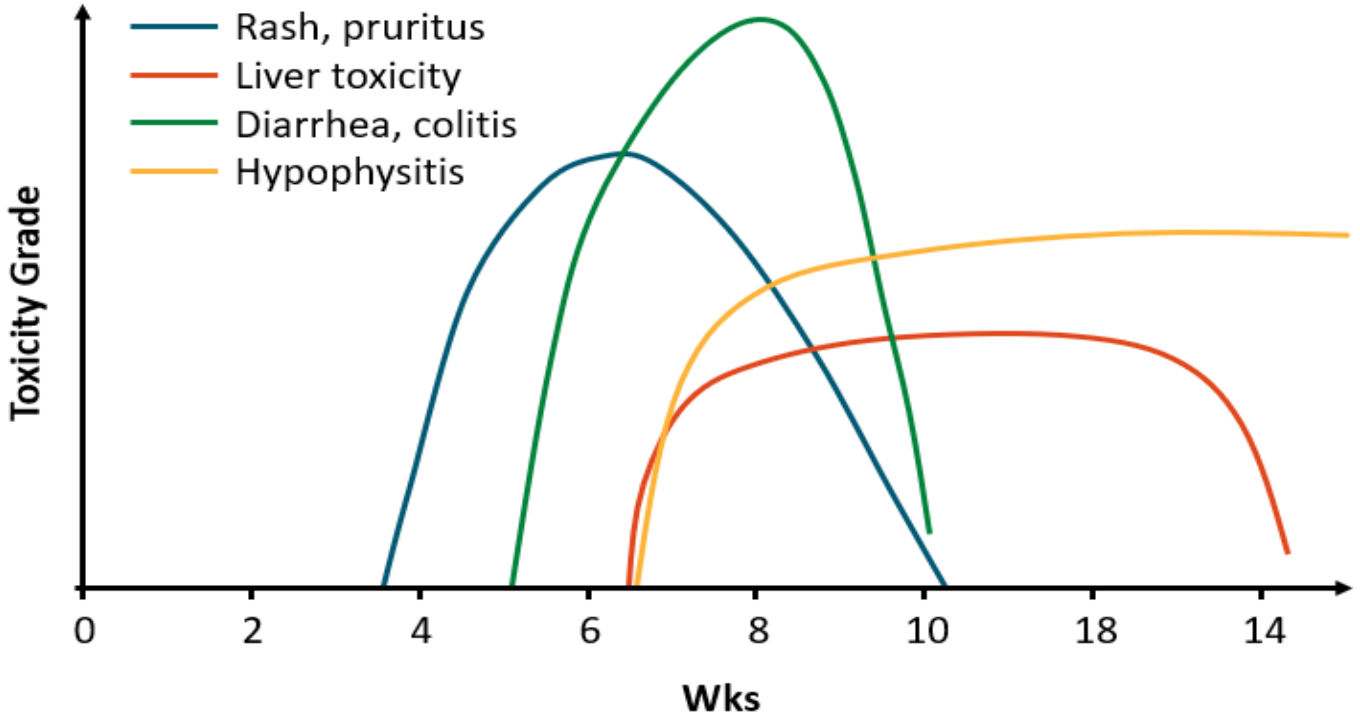
- Dose reduction is not a recommended strategy
- Avoid delays in recognition and intervention

  Education & Education & Education

  early detection



Most irAEs Are Reversible With Immunosuppression/ Steroids



Monitoring

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Management of Immune Checkpoint Inhibitor-Related Toxicities

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PRINCIPLES OF ROUTINE MONITORING FOR IMMUNE CHECKPOINT INHIBITORS

Pre-Therapy Assessment[a]	Monitoring Frequency[b]	Evaluation for Abnormal Findings/Symptoms
Clinical • Physical examination • Patient and relevant family history of any autoimmune/organ-specific disease, endocrinopathy, or infectious disease (ID) • Neurologic examination • Bowel habits (typical frequency/consistency) • ID screening (human immunodeficiency virus [HIV]; hepatitis A, B, C) as indicated	Clinical examination at each visit with adverse event (AE) symptom assessment	Follow-up testing based on findings, symptoms
Imaging • Cross-sectional imaging • Brain MRI if indicated	Periodic imaging as indicated	Follow-up testing as indicated based on imaging findings
General blood work • Complete blood count (CBC) (with differential if indicated) • Comprehensive metabolic panel (CMP)	Repeat prior to each treatment or every 4 weeks during immunotherapy, then in 6–12 weeks or as indicated	HbA1c for elevated glucose
Dermatologic (ICI_DERM-1) • Examination of skin and mucosa if history of immune-related skin disorder	Conduct/repeat as needed based on symptoms	Consider dermatology referral. Monitor affected skin and lesion type; photographic documentation. Skin biopsy if indicated.
Pancreatic (ICI_ENDO-1) • Baseline testing is not required	No routine monitoring needed if asymptomatic	Amylase, lipase, and consider abdominal CT with contrast or MRCP for suspected pancreatitis
Thyroid (ICI_ENDO-2) • Thyroid-stimulating hormone (TSH), free thyroxine (FT4)	Every 4–6 weeks during immunotherapy, then follow-up every 12 weeks as indicated	ICI_ENDO-2 and ICI_ENDO-3

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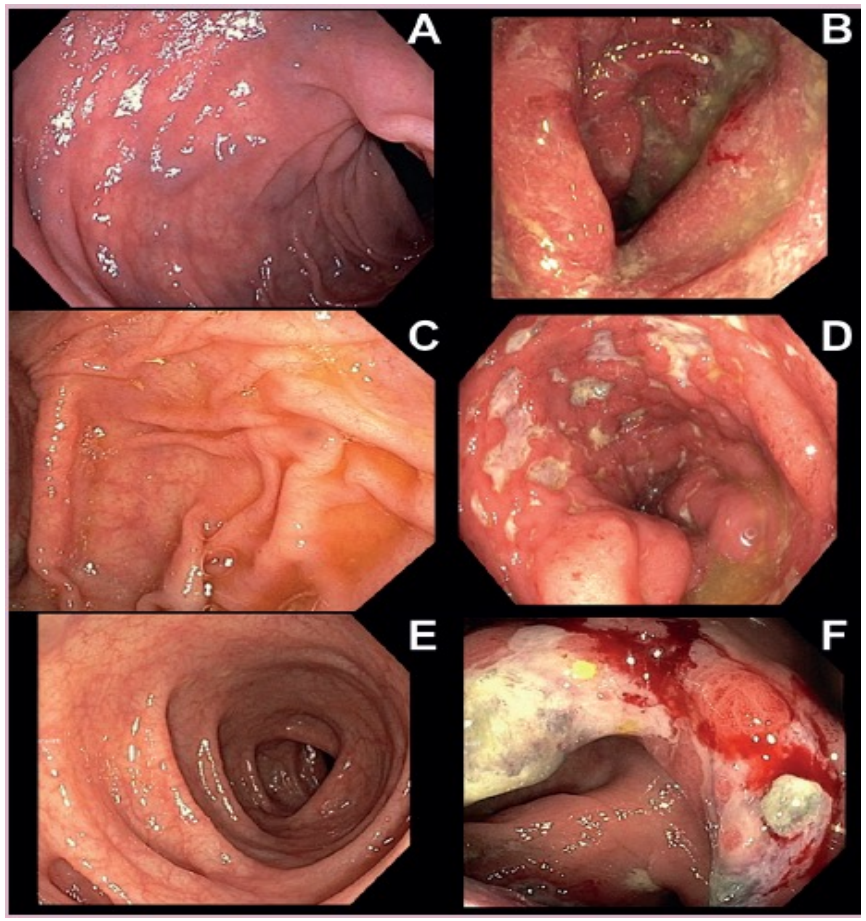
Pre-Therapy Assessment[a]	Monitoring Frequency[b]	Evaluation for Abnormal Findings/Symptoms
Pituitary/Adrenal (ICI_ENDO-4) • Consider serum cortisol (morning preferred) and thyroid function as above	Consider repeating every 4–6 weeks during immunotherapy (immuno-oncology [IO]-only regimens[c]), then follow-up every 12 weeks as indicated	Morning serum cortisol, adrenocorticotropic hormone (ACTH), TSH, FT4, luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, estradiol (premenopausal individuals), and cosyntropin stimulation test only as indicated
Pulmonary (ICI_PULM-1) • Oxygen saturation (resting and with ambulation) • Consider pulmonary function tests (PFTs) with diffusion capacity for patients who are high risk (eg, interstitial lung disease on imaging, chronic obstructive pulmonary disease [COPD], previous suspected treatment-related lung toxicity) • In the absence of prior imaging, consider a chest x-ray	Repeat oxygen saturation tests based on symptoms	Chest CT with contrast to evaluate for pneumonitis, biopsy, or bronchoscopy with bronchoalveolar lavage (BAL) if needed to exclude other causes
Cardiovascular (ICI_CARDIO-1) • Consider baseline electrocardiogram (ECG) • Consider high-sensitivity troponin and N-terminal prohormone B-type natriuretic peptide (NT-proBNP) • Individualized assessment in consultation with cardiology as indicated	Consider periodic testing for those with abnormal baseline or symptoms[d]	Individualized follow-up in consultation with cardiology as indicated
Musculoskeletal (ICI_MS-1) • Joint examination/functional assessment as needed for patients with pre-existing disease	No routine monitoring needed if asymptomatic	Consider rheumatology referral. Depending on clinical situation, consider C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), or creatine kinase (CK)

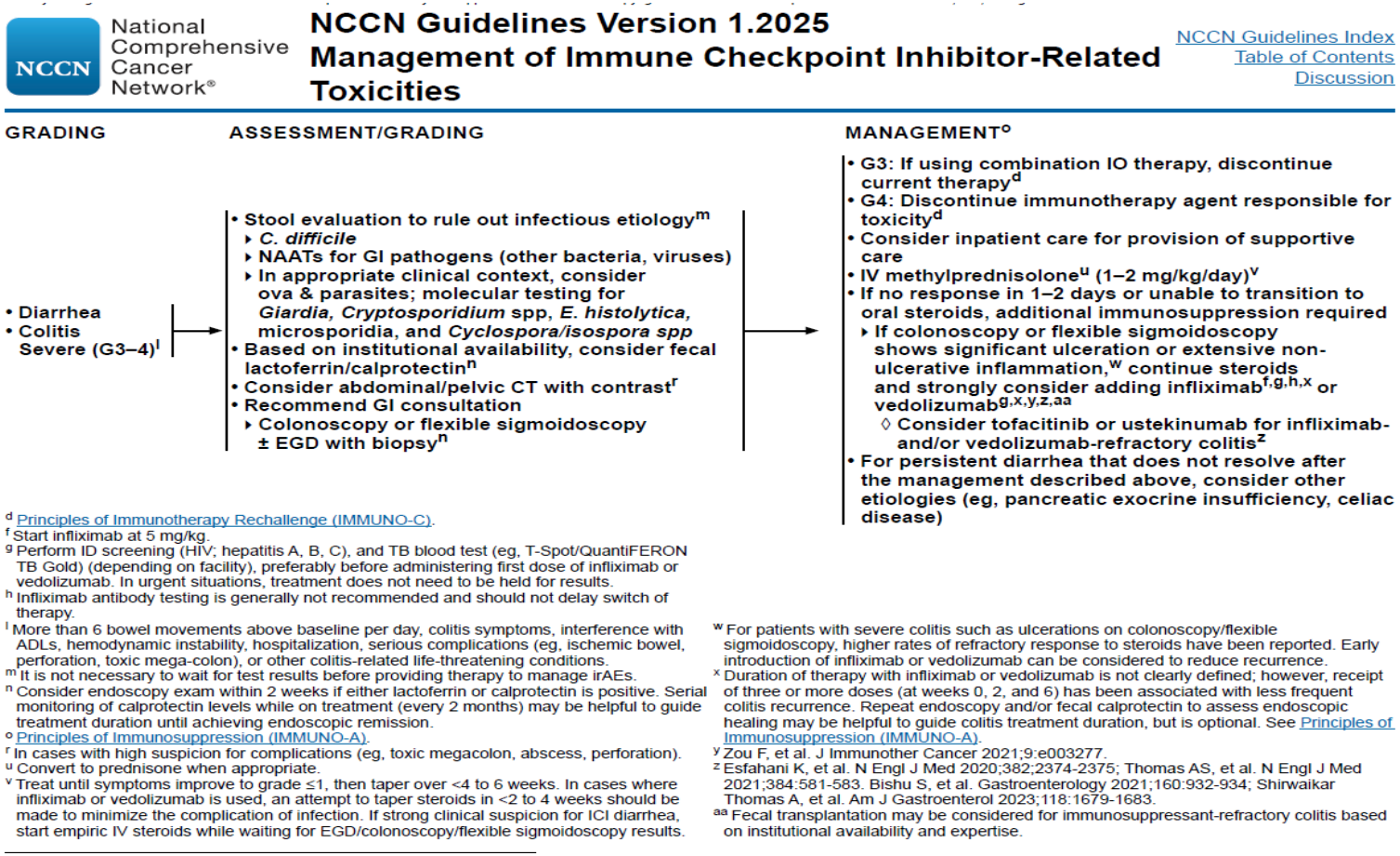
Colitis in Patients Treated With ICIs



Grade 2 diarrhea with swollen, erosive, and friable mucosa

Grade 3 diarrhea with deeply red colon where vascular pattern partially absent, mucosa severely friable, multiple ulcers

Colitis in Patients Treated With ICIs



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GRADING

- Diarrhea
- Colitis
  Severe (G3–4)[l]

ASSESSMENT/GRADING

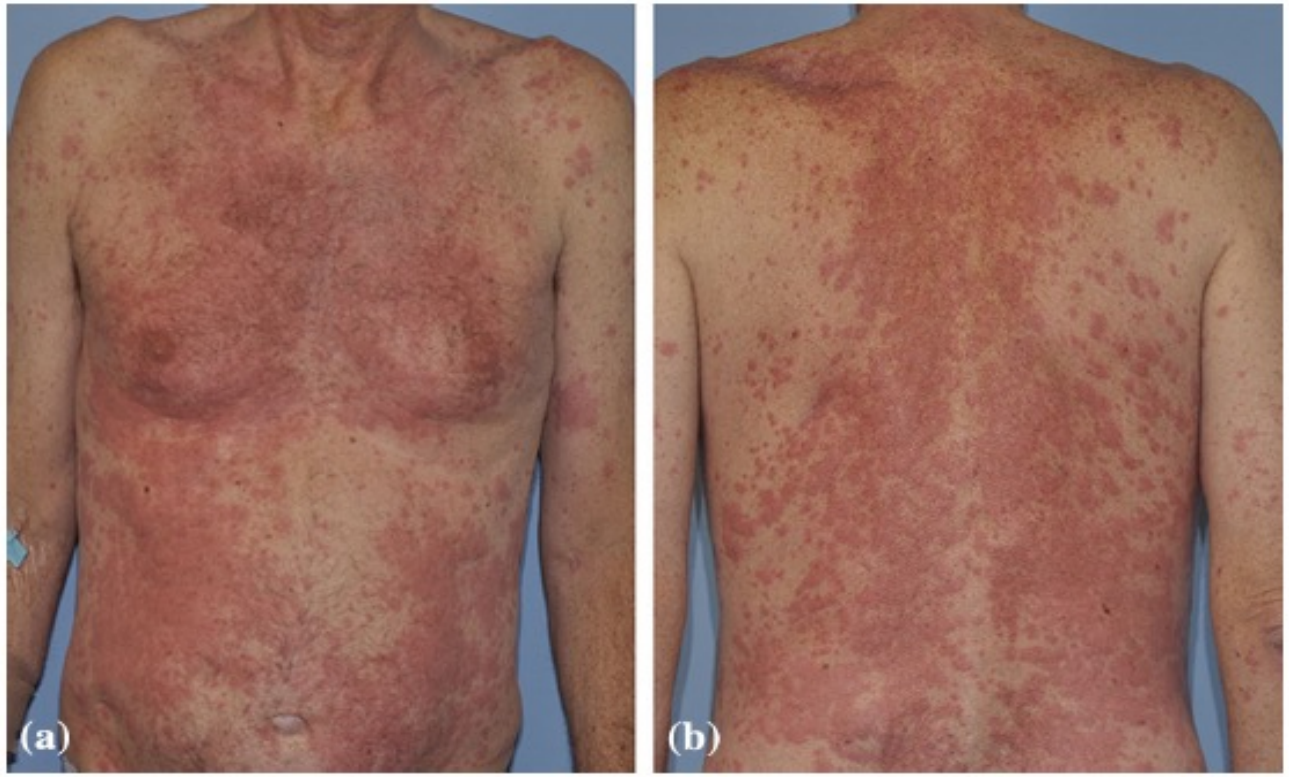
- Stool evaluation to rule out infectious etiology[m]
  - *C. difficile*
  - NAATs for GI pathogens (other bacteria, viruses)
  - In appropriate clinical context, consider ova & parasites; molecular testing for *Giardia, Cryptosporidium* spp, *E. histolytica,* microsporidia, and *Cyclospora/isospora spp*
- Based on institutional availability, consider fecal lactoferrin/calprotectin[n]
- Consider abdominal/pelvic CT with contrast[r]
- Recommend GI consultation
  - Colonoscopy or flexible sigmoidoscopy ± EGD with biopsy[n]

MANAGEMENT[o]

- G3: If using combination IO therapy, discontinue current therapy[d]
- G4: Discontinue immunotherapy agent responsible for toxicity[d]
- Consider inpatient care for provision of supportive care
- IV methylprednisolone[u] (1–2 mg/kg/day)[v]
- If no response in 1–2 days or unable to transition to oral steroids, additional immunosuppression required
  - If colonoscopy or flexible sigmoidoscopy shows significant ulceration or extensive non-ulcerative inflammation,[w] continue steroids and strongly consider adding infliximab[f,g,h,x] or vedolizumab[g,x,y,z,aa]
    - ◊ Consider tofacitinib or ustekinumab for infliximab- and/or vedolizumab-refractory colitis[z]
- For persistent diarrhea that does not resolve after the management described above, consider other etiologies (eg, pancreatic exocrine insufficiency, celiac disease)

[d] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[f] Start infliximab at 5 mg/kg.
[g] Perform ID screening (HIV; hepatitis A, B, C), and TB blood test (eg, T-Spot/QuantiFERON TB Gold) (depending on facility), preferably before administering first dose of infliximab or vedolizumab. In urgent situations, treatment does not need to be held for results.
[h] Infliximab antibody testing is generally not recommended and should not delay switch of therapy.
[l] More than 6 bowel movements above baseline per day, colitis symptoms, interference with ADLs, hemodynamic instability, hospitalization, serious complications (eg, ischemic bowel, perforation, toxic mega-colon), or other colitis-related life-threatening conditions.
[m] It is not necessary to wait for test results before providing therapy to manage irAEs.
[n] Consider endoscopy exam within 2 weeks if either lactoferrin or calprotectin is positive. Serial monitoring of calprotectin levels while on treatment (every 2 months) may be helpful to guide treatment duration until achieving endoscopic remission.
[o] Principles of Immunosuppression (IMMUNO-A).
[r] In cases with high suspicion for complications (eg, toxic megacolon, abscess, perforation).
[u] Convert to prednisone when appropriate.
[v] Treat until symptoms improve to grade ≤1, then taper over <4 to 6 weeks. In cases where infliximab or vedolizumab is used, an attempt to taper steroids in <2 to 4 weeks should be made to minimize the complication of infection. If strong clinical suspicion for ICI diarrhea, start empiric IV steroids while waiting for EGD/colonoscopy/flexible sigmoidoscopy results.
[w] For patients with severe colitis such as ulcerations on colonoscopy/flexible sigmoidoscopy, higher rates of refractory response to steroids have been reported. Early introduction of infliximab or vedolizumab can be considered to reduce recurrence.
[x] Duration of therapy with infliximab or vedolizumab is not clearly defined; however, receipt of three or more doses (at weeks 0, 2, and 6) has been associated with less frequent colitis recurrence. Repeat endoscopy and/or fecal calprotectin to assess endoscopic healing may be helpful to guide colitis treatment duration, but is optional. See Principles of Immunosuppression (IMMUNO-A).
[y] Zou F, et al. J Immunother Cancer 2021;9:e003277.
[z] Esfahani K, et al. N Engl J Med 2020;382:2374-2375; Thomas AS, et al. N Engl J Med 2021;384:581-583. Bishu S, et al. Gastroenterology 2021;160:932-934; Shirwaikar Thomas A, et al. Am J Gastroenterol 2023;118:1679-1683.
[aa] Fecal transplantation may be considered for immunosuppressant-refractory colitis based on institutional availability and expertise.

Dermatologic Reactions in Patients Treated With Immune Checkpoint Inhibitors



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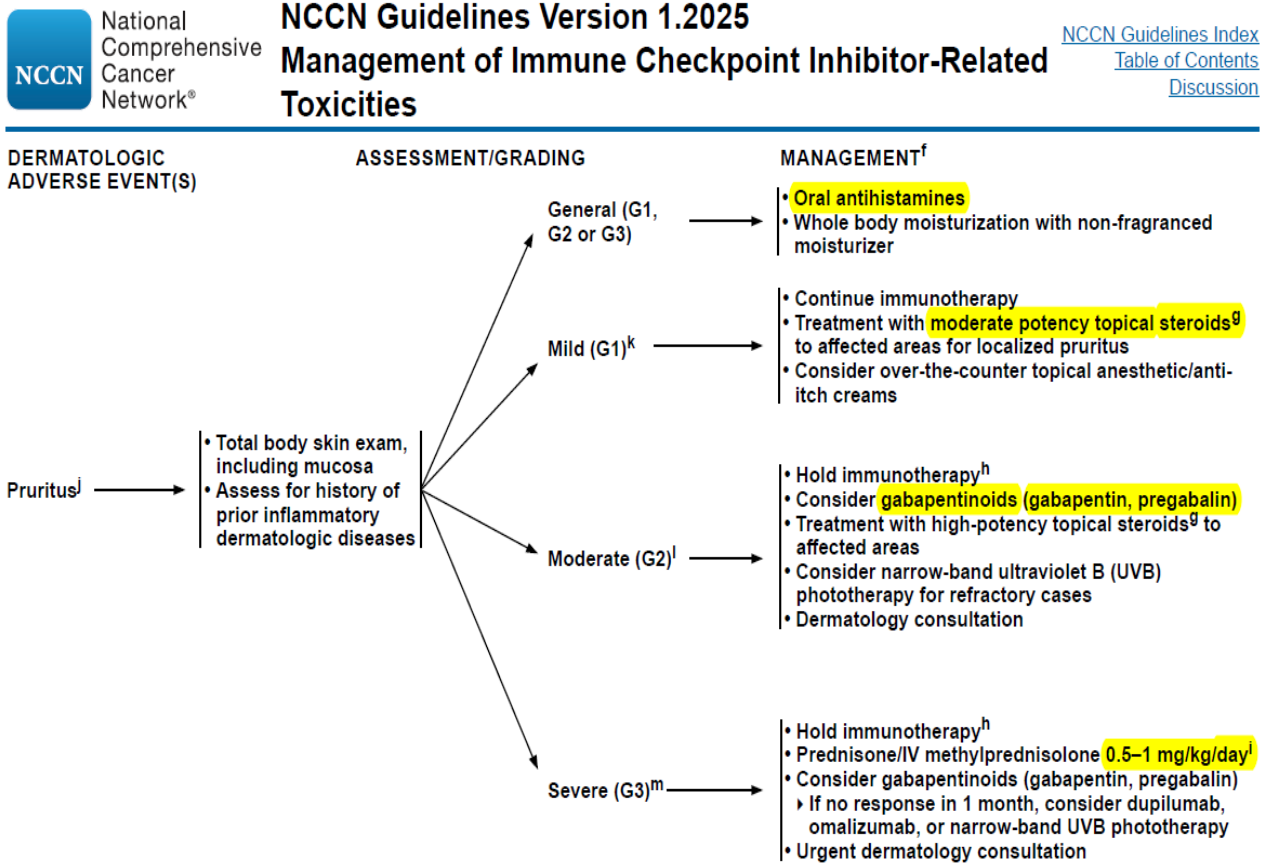

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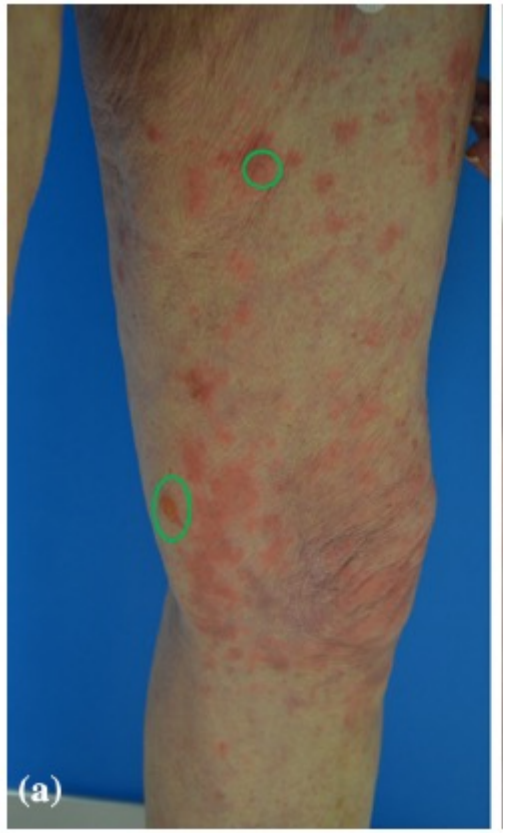
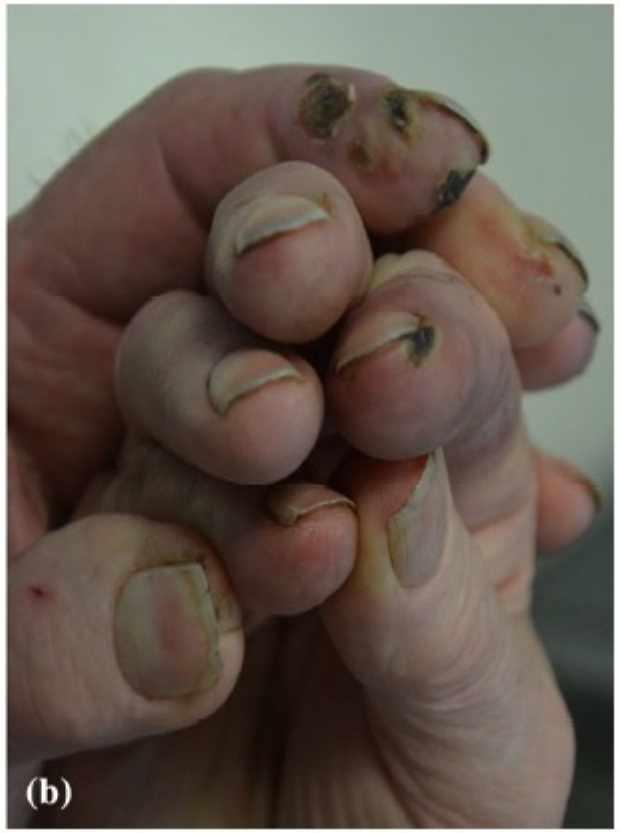


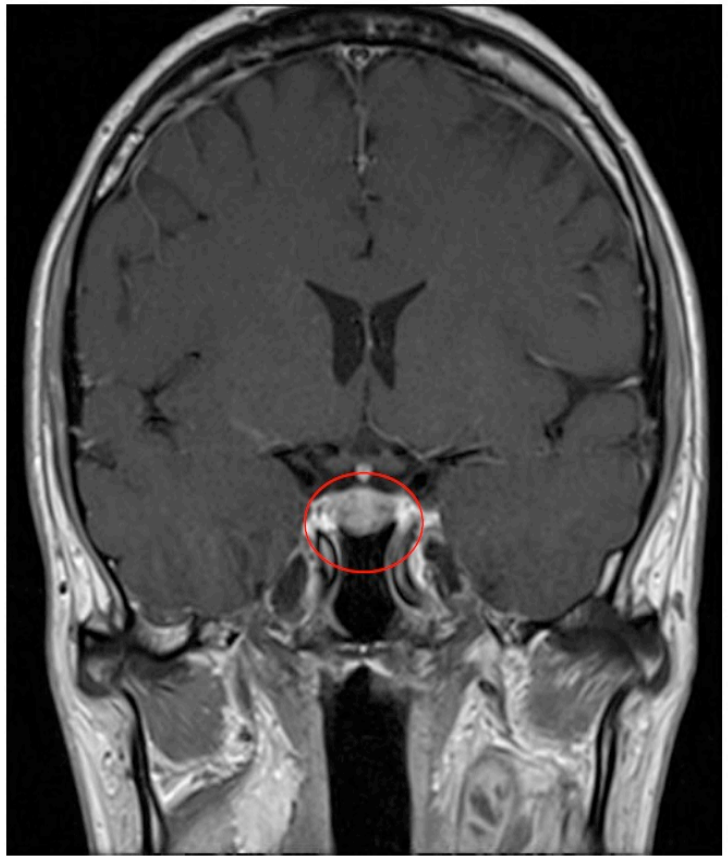


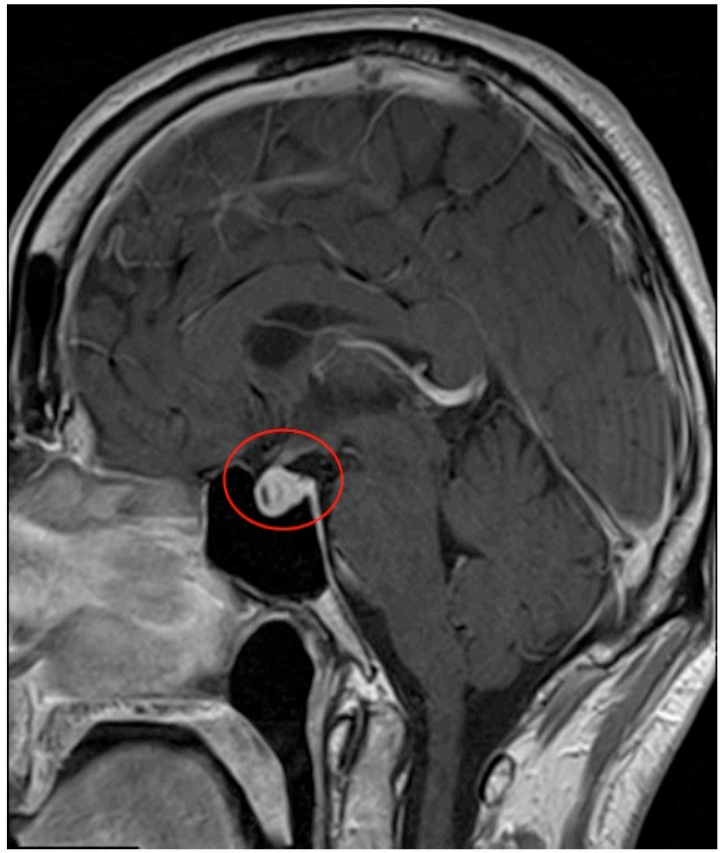
Case

- 53 year old man with metastatic melanoma BRAF WT 4th cycles of ipilimumab and nivolumab 3 weeks ago

- Headache
- Visual disturbance
- Fatigue
- Nausea and vomiting

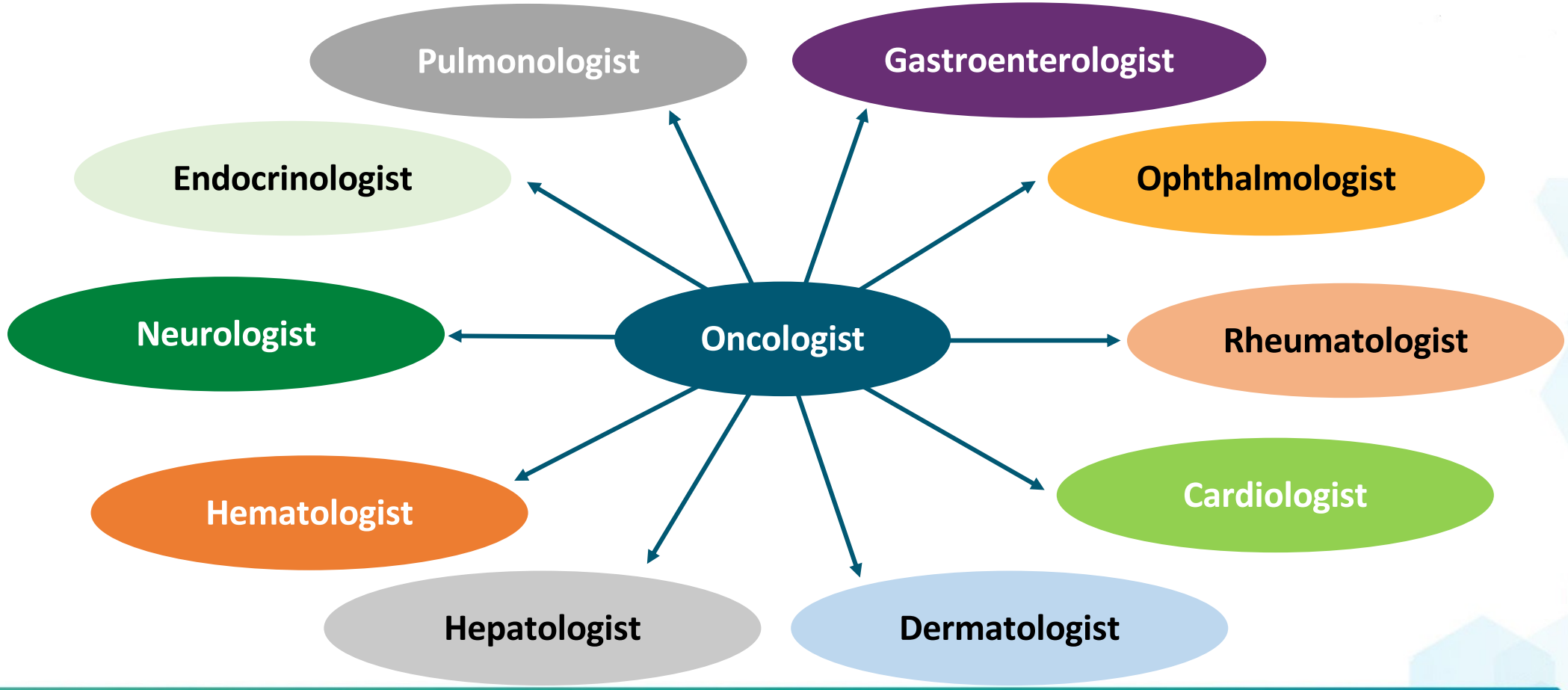
MRI





- Endocrinology consult
- Hydrocortisone 20 mg TDS
- Oral prednisolone 1 mg /kg

Multidisciplinary Approach to the Management of Patients



Conclusions

- More patients are being treated with ICIs as indications expand to new malignancies, earlier lines of therapy, and earlier stages of disease
- ICIs can cause irAEs by activating immune cells in nontumor tissues
  - **irAEs can occur after discontinuing ICI**
- irAEs most commonly presenting to emergency department are diarrhea, colitis, dermatitis, pneumonitis, hypophysitis

- When a patient with cancer history presents to clinic:
  - Ask about immunotherapy treatment, autoimmune conditions
  - Consult promptly with specialists for affected organ systems
  - Manage based on severity of symptoms by providing supportive care, holding/discontinuing immunotherapy, and administering corticosteroids, as appropriate
  - Make use of resources on identification and management of irAEs, including NCCN Guidelines, ASCO / ESMO guidelines

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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Management of Immunotherapy-Related Toxicities

Version 1.2025 — December 20, 2024

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NCCN recognizes the importance of clinical trials and encourages
Trials should be designed to maximize inclusiveness a

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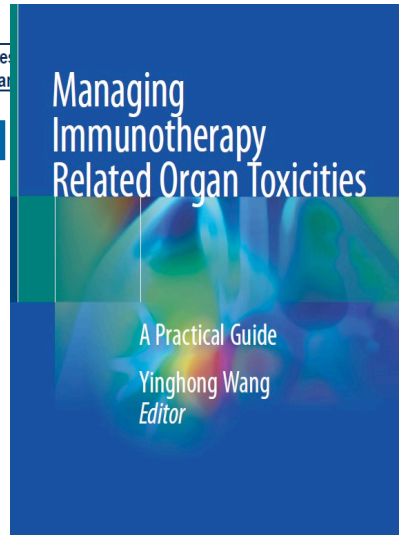

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SPECIAL ARTICLE

Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

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