Nivolumab (Opdivo®) is an anti-programmed death receptor-1 (PD-1) monoclonal antibody checkpoint inhibitor. PD-1 is a negative regulator of T-cell activation and proliferation, meaning it “turns the immune response off,” essentially acting as a brake. This type of inhibition is necessary to prevent excessive immune reaction and autoimmunity. For this reason, PD-1 and other regulators acting in this manner are known as immune checkpoints. We now understand that some tumors can exploit the PD-1 pathway, enabling them to evade an immune response. Nivolumab selectively binds to PD-1, thus blocking the inhibitory pathway, allowing the immune response to occur.

Nivolumab is indicated as monotherapy for the treatment of unresectable or metastatic (advanced) melanoma and for various other cancer types. Nivolumab is also indicated in combination with ipilimumab (Yervoy®) for the treatment of unresectable or metastatic melanoma (discussed in a separate nursing tool).

In December, 2017, the FDA approved nivolumab as an adjuvant treatment for patients with melanoma with involvement of lymph nodes (Stage III) or metastatic (Stage IV) disease who have undergone complete resection.

This document is part of an overall nursing toolkit intended to assist nurses in optimizing management of melanoma in patients receiving newer anti-melanoma therapies.
Nivolumab is a clear to slightly opalescent, colorless to pale-yellow solution. Discard the vial if the solution is cloudy, discolored, or contains extraneous particulate matter (other than a few translucent-to-white, proteinaceous particles).

To prepare the dose, withdraw the required volume of nivolumab and transfer it into an intravenous container. This should be diluted with either 0.9% Sodium Chloride injection, USP, or 5% Dextrose, USP to prepare an infusion with a final concentration ranging from 1 mg/ml to 10 mg/ml.

Mix the diluted solution by gentle inversion. Do not shake.

Do not coadminister nivolumab with other drugs through the same intravenous line.

Nivolumab is classified as an irritant and may be safely administered via a central or peripheral line. It is important to ensure IV access before administration.

Nivolumab should be administered through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding in-line filter (pore size of 0.2 - 1.2 micrometers).

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For unresectable or metastatic melanoma, the recommended dose of nivolumab (Opdivo®) is 240 mg administered as an intravenous infusion over 60 minutes every 2 weeks or 480 mg every 4 weeks until disease progression or unacceptable toxicity.

For adjuvant treatment for patients with melanoma with involvement of lymph nodes (Stage III) or metastatic (Stage IV) disease who have undergone complete resection, the recommended dose of nivolumab (Opdivo®) is 240 mg administered as an intravenous infusion over 60 minutes every 2 weeks or 480 mg every 4 weeks until disease recurrence or unacceptable toxicity.

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For unresectable or metastatic melanoma, the recommended dose of nivolumab (Opdivo®) is 240 mg administered as an intravenous infusion over 60 minutes every 2 weeks or 480 mg every 4 weeks until disease progression or unacceptable toxicity.
Because nivolumab is an immunotherapy that works by enhancing the patient’s immune system, most adverse reactions associated with nivolumab are related to overactivity of the patient’s immune system (ie, immune-related adverse events [irAEs]). Various organ systems (often more than one) or tissues may be affected.

- **Key to toxicity management:**
  - Proactive assessment for early signs/symptoms of toxicity
  - Prompt intervention
  - irAEs are typically managed with selective use of steroids
  - In rare instances, toxicity may be steroid refractory, and additional immunosuppressive agents (mycophenolate mofetil, cyclophosphamide, etc) may be necessary
  - Nivolumab will likely be held or discontinued depending on the severity and/or persistence of the irAE
  - Referral to organ specialist should be considered, given that unique testing and management strategies may be required

- irAEs associated with nivolumab treatment can be categorized as those that are most common, less common but serious, and others that are easily overlooked

- Table 1 lists these irAEs and the corresponding Care Step Pathways in Appendix 1. Other adverse events associated with nivolumab are shown in Appendix 2

### Table 1. Care Step Pathways for the management of immune-related AEs associated with nivolumab monotherapy.

<table>
<thead>
<tr>
<th>irAE category</th>
<th>Examples</th>
<th>Location</th>
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<td>Skin toxicities (pruritis, rash, etc)</td>
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<td>Easily overlooked</td>
<td>Arthralgia/arthritis</td>
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<td>Neuropathy</td>
<td></td>
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<tr>
<td></td>
<td>Nephritis</td>
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</tbody>
</table>
CLINICAL PEARLS

• PD-L1 status or elevated expression in not a prerequisite for nivolumab treatment of advanced melanoma

• It is important to monitor laboratory values at the start of treatment, periodically during treatment, and as indicated clinically

• Nivolumab-related irAEs may occur at any time, including after treatment completion or discontinuation

• Patients sometimes experience signs/symptoms that they think are due to “flu” or a cold, but that actually represent an irAE or an infusion reaction

• Endocrinopathies often present with vague symptoms (fatigue, headache, and/or depression) that can easily be overlooked or initially misdiagnosed. Hypervigilance and follow-up is important on the part of both nurses and patients

• IrAEs may become apparent upon tapering of corticosteroids, since they can be suppressed or masked by immunosuppressive therapy. Patients should be advised to be on the lookout for early signs of irAEs during the tapering period

• Endocrinopathies tend to occur somewhat more commonly with nivolumab or other PD-1 inhibitor therapies than with ipilimumab monotherapy

• Unlike other irAEs, endocrinopathies usually do not resolve and may require lifelong hormone replacement therapy

• Nurses should encourage patients to carry information about their nivolumab regimen with them at all times. This might be the nivolumab-specific wallet card, or at least emergency phone numbers and a list of side effects associated with the regimen. You may suggest that they paperclip the wallet and insurance cards together so information about their regimen will be shared whenever they show the insurance card

• Advise patients to take pictures of any skin lesions for documentation
Q. How long will patients stay on nivolumab?

A. The prescribing information indicates until disease progression or unacceptable toxicity. For metastatic disease, the interpretation of these criteria varies from institution to institution and from provider to provider. In the adjuvant setting, nivolumab is also used until disease recurrence or unacceptable toxicity for up to 1 year.

Q. Are there standard dosage reductions for irAEs associated with nivolumab?

A. There are no standard dosage reductions for irAEs associated with nivolumab. The dose is either held until the irAE resolves sufficiently (typically to Grade 0 or Grade 1) or, if the irAE is severe enough, nivolumab is discontinued permanently.

Q. I have experience using nivolumab for lung cancer. Is the safety profile different in those patients' vs melanoma patients?

A. Generally, the safety profile of nivolumab is similar across tumor types. However, the context may be different—patients with other tumor types may have differing comorbidities or underlying organ dysfunction. For example, lung cancer patients may have underlying lung disease that will exacerbate shortness of breath associated with pneumonitis.

Q. How do I counsel my patients about immunizations?

A. That's a logical question, given that the checkpoint inhibitors alter the immune response. Advise your patients not to receive live vaccines (eg, measles, mumps, and rubella and the varicella vaccine [Zostavax®]) because they have not been evaluated in this setting. The use of attenuated vaccines has been and continues to be evaluated. Counsel patients to discuss all immunizations with the oncology team prior to administration so the benefits and risks can be weighed on an individual basis. For example, Shingrix®, approved in 2017, is an attenuated (non-live) varicella vaccine, which can be discussed with the oncology team if a recommendation is being made for the patient to receive the injection series.
PATIENT RESOURCES

Financial Assistance
BMS Access Support
1 (800) 861-0048
http://www.bmsaccesssupport.bmscustomerconnect.com/patient

Additional Information Resources
AIM at Melanoma Foundation (Nurse on Call, patient symposia, drug resources, etc)
http://www.AIMatMelanoma.org
American Cancer Society Resource Section


• Opdivo patient alert card (wallet card) and other resources. http://www.opdivo.com/metastatic-melanoma/patient-caregiver-support/downloadable-resources


Click here for downloadable action plans to customize for your patients
Skel Toxicities  Page 2 of 2

**Management**

- Identify barriers to adherence
- Recognize and address understanding of skin care
- Address skin symptoms
- Avoid sun exposure
- Cool temperature
- Keep fingernails short
- Use tepid water
- Avoid hot water; bathe or shower
- Topical corticosteroids will be used in pemphigus vulgaris, required for skin involvement
- Oral corticosteroids will be used in confirmed SJS or TEN
- Immunotherapy (e.g., pembrolizumab or nivolumab) to be withheld for any Grade 3/4 event, and nivolumab for Grade 4 rash or confirmed SJS or TEN
- Day 1: Ultraviolet light at least 4 times greater than prior dose
- Consider dermatology consultation

**Grade 4 (Severe or Life-Threatening)**

- Grading Toxicity
  - **Risk of opportunistic infection and need for hospitalization**
  - **Side effects of high-dose steroids**
  - **Rationale for prolonged steroid taper**
  - **Interventions in at-risk patients**

**Overall Strategy**

- **Assess for evidence of rash:** patient about new medications, Herbs, supplements, alternative/complementary therapies, etc.
- **Identify barriers to adherence**
- **Simplify and modify treatment plan**
- **Recommendations and rationale**
- **Understand of skin care**
- **Assess patient and family understanding of prevention strategies and rationale**
- **Identify potential barriers to adherence, specifically compliance with steroids when transitioned to oral corticosteroids**
- **Reframing products prior to application**
- **Gentle skin care**
- **Cool cloth applications**
- **Moisturizers with ceramides and lipids are advised;**
- **i.e. petroleum jelly, can be used**
- **Appropriate administration of non-steroidal moisturizers or emollients containing humectants (urea, glycerin)**
- **Consider dermatology consultation**
- **Advise vigorous skin care**
- **Moisturizers and emollients**
- **Intervention indicated**

**TEN** = Toxic epidermal necrolysis

**STEVENS-JOHNSON SYNDROME**

**BSA** = Body surface area

**ADLS** = Activities of daily living; **ADL**

---

**R E D F A G S:**

- **Concern for suprainfection**
- **Oral involvement**
- **Extensive rash (>50% BSA), or rapidly progressive**
Gastrointestinal Toxicity Page 1 of 3

Overall Strategy:

Management

Severe abdominal pain or mucus in stool

Diarrhea

Increased frequency, loose, large volume, or liquid stools

Grading Toxicity

Diarrhea (increased frequency, loose, large volume, or liquid stools)

Grade 3 (Severe)

Grade 2 (Moderate)

Grade 1 (Mild)

Colitis (potentially life-threatening)

Life-threatening (e.g., perforation, bleeding, ischemic necrosis, toxic megacolon)

Diagnostic testing: blood, stool panel, or imaging

Care Step Pathway - Gastrointestinal Toxicity: Diarrhea and Colitis

Nursing Assessment

Recognize:

- Decreased appetite or food aversions
- Nausea or vomiting
- Diarrhea
- Change in bowel habits
- Pain, tenderness, bloating
- Perianal signs of bowel perforation
- Constitutional symptoms
- Changes in weight or fluid intake

Listen:

- Does the patient appear in distress?
- Does the patient appear dehydrated?
- Has the patient lost weight?

Look:

- Rectal examination
- Stool, urine, and blood cultures
- Laboratory values

Grade 1 (Mild)

Grade 2 (Moderate)

Grade 3 (Severe)

Grade 4 (Potentially Life Threatening)

Grade 5 (Death)

Factors that may increase risk of gastrointestinal toxicities:

- Immunosuppressive therapy
- Prior history of inflammatory bowel disease
- Age
- Performance status

Supportive medications for symptomatic management:

- Steroids to be tapered slowly over at least 4 weeks
- Advance diet slowly as steroids reduced to low doses
- Avoid laxatives or stool softeners
- Decrease fiber, uncooked fruit and vegetables, red meats

Grade 3: Pembrolizumab or nivolumab to be withheld

Grade 2: Pembrolizumab or nivolumab to be withheld

Grade 1: Pembrolizumab or nivolumab to be held

Diet modification:

- fiber and low residue (BRAT diet)
- Institute bland diet low in fiber, residue, and fat (BRAT [Bananas, Rice, Applesauce, Toast] diet)
- Avoid fats, dairy, oil, caffeine, alcohol, sugar
- Decrease fiber, uncooked fruit and vegetables, red meats

Immunotherapy to be withheld

Infliximab infusion delay may have life-threatening (severe or life-threatening)

Dose of steroids to be increased:

- Does the patient appear in distress?
- Does the patient appear dehydrated?
- Has the patient lost weight?
- Look:

Institute bland diet low in fiber, residue, and fat (BRAT [Bananas, Rice, Applesauce, Toast] diet)

Infectious vs immune-related adverse event

- Fever
- Change in weight
- Change in appetite
- Change in bowel habits
- Decrease in energy
- Increase in fatigue

Look:

- Does the patient appear in distress?
- Does the patient appear dehydrated?
- Has the patient lost weight?
- Look:

Recognize:

- Decreased appetite or food aversions
- Nausea or vomiting
- Diarrhea
- Change in bowel habits
- Pain, tenderness, bloating
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Infectious vs immune-related adverse event

- Fever
- Change in weight
- Change in appetite
- Change in bowel habits
- Decrease in energy
- Increase in fatigue

Look:

- Does the patient appear in distress?
- Does the patient appear dehydrated?
- Has the patient lost weight?

Look:
**Supportive medications for symptomatic management:**

- Steroids (dexamethasone, 1 mg/kg IV or P.O.; prednisone 1-2 mg/kg/day)
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Probiotics
- Antimotility agents
- Antacids

**RED FLAGS:**

- Fever and/or chills
- Malaise
- Cough
- Dysuria
- Jaundice
- Observational symptoms: jaundice, oozing, or bleeding

**Management (Including Anticipatory Guidance):**

**Grade 1 (Mild):**

- Rule out infections, non-infectious, disease-related etiologies

**Grade 2 (Moderate):**

- Consider gastroenterology consult for possible intervention

**Grade 3 (Severe):**

- Consider gastroenterology consult for possible intervention

**Grade 4 (Potentially Life-Threatening):**

- Hospitalization

**Grade 5 (Death):**

- See melanoma nursing pathway for complete grading criteria

---

**Overall Strategy:**

- Early identification and evaluation of patient symptoms
- Compare baseline assessment: grade & document bowel frequency

---

**Nursing Implementation:**

- So diarrhea stool thereafter, with a maximum of 6 per day
- Supportive medications for symptomatic management:
  - Steroids* to be tapered slowly over at least 4 weeks
  - Advance diet slowly as steroids* reduced to low doses

**Diet modifications:**

- (Moderate) persistent or relapsed symptoms with steroid*
  - Avoid laxatives or stool softeners
  - May continue immunotherapy
  - Infliximab (Remicade®) 5 mg/kg infusion may be considered
  - Diarrhea (increased frequency, loose, large volume, or liquidy stools)
  - Fatigue
  - Decreased appetite or food aversions

---

**Immunotherapy:**

- Tapers should consider patient’s current symptom profile
- Grade symptom & determine level of care and interventions required
- Early identification and evaluation of patient symptoms
- Compare baseline assessment: grade & document bowel frequency

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**Gastrointestinal Toxicity Page 2 of 3**

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Gastrointestinal Toxicity

**RED FLAGS**:
- Fever
- Abdominal pain
- More frequent stools, consistency change from loose to liquid
- Bloating, nausea
- Change in gastrointestinal function, decreased appetite

**ADLS = activities of daily living; PD = programmed cell death protein 1**

If upper or lower GI symptoms persist >5–7 days
- 
  - Grade symptom & determine level of care and interventions required
  - Early identification and evaluation of patient symptoms
  - Early intervention with lab work and office visit if colitis symptoms are suspected
  - DxC symptoms at determining level of care and interventions required
  - Compare baseline assessment grade x document bowel frequency

**Management**
- Consider antimicrobial prophylaxis (such as azithromycin or ciprofloxacin) double dose N/W/F, single dose if used daily or alternative if sulfa-allergic
- Avoid alcohol/acetaminophen or other hepatotoxins
- Review steroid medication side effects: mood changes (anger, reactive, hyperaware, euphoric, mania), increased appetite, interrupted sleep, oral thrush, fluid retention
- Use caution with analgesics (opiates) and anti-diarrheal medications
- Provide anti-diarrheals: Imodium® (loperamide) or Lomotil®
- Confirm infectious vs immune related adverse event
- Rule out infectious, non-infectious, disease-related etiologies

**Grade symptom & determine level of care interventions required**

*Steroid taper instructions/calendar as a guide but not an absolute

---

**Care Step Pathway**

**Immunotherapy to be held**

- Infliximab infusion delay may have life-threatening consequences
- PPD (tuberculin) testing not required in this setting
- Avoid with bowel perforation or sepsis
- May require ≥1 infusion to manage symptoms

**Immunotherapy to be discontinued if**

- Grade 2 symptoms
- Grade 3 (Severe) persistent or relapsed symptoms with steroid
- *Advance diet slowly as steroids are tapered, reduced to low doses

**Grade 4 (Potentially Life Threatening)**

- Ipilimumab and/or PD-1 inhibitor to be held
- Diet modification:
  - Very strict with acute symptoms: clear liquids; very bland, low residue (BRAT diet)
  - Then ≥4 fruits/vegetables, red meats, fats, dairy, oil, caffeine, alcohol, sugar
  - Long-term illness/loss of appetite

**Grade 5 (Death)**

- ipilimumab or nivolumab, or for inability to reduce steroid dose to ≤1 or patient's baseline (ipilimumab, pembrolizumab, nivolumab)
- Infliximab infusion delay may have life-threatening consequences
- May require ≥1 infusion to manage symptoms

**Immunotherapy to be withheld until**

- Grade symptom & determine level of care and interventions required
- Early identification and evaluation of patient symptoms
- Early intervention with lab work and office visit if colitis symptoms are suspected

**Nursing Implementation**

- Early identification and evaluation of patient symptoms
- Early intervention with lab work and office visit if colitis symptoms are suspected
- DxC symptoms at determining level of care and interventions required
- Compare baseline assessment grade x document bowel frequency

---

**Immunotherapy to be continued if**

- Grade ≤1 or patient's baseline (ipilimumab, pembrolizumab, nivolumab)
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  - Then ≥4 fruits/vegetables, red meats, fats, dairy, oil, caffeine, alcohol, sugar
  - Long-term illness/loss of appetite
Nutrition referral if appropriate
- Monitor hydration status
- Monitor weight

Dexamethasone oral solution
- Corticosteroid rinses
- Diphenhydramine/lidocaine/simethicone
- "Miracle Mouthwash":
  - 2% morphine mouthwash

Encourage soft, bland non-acidic foods
- bicarbonate dissolved in 4 cups of water
  - ½ tsp salt and 2tbsps sodium bicarbonate rinses
  - or 1 tsp baking soda in 8 ounces of water

If unable to tolerate brushing, advise chlorhexidine gluconate 0.12% or sodium bicarbonate rinses
- Increase frequency of brushing to Q4
- Vigilant oral hygiene

Mucositis:
- Cevimeline HCI

Identify barriers to adherence
- Pharmacologic
- and rationale for interventions as well as treatment discontinuation

Natural lemon
- Sugarless hard candies
- Sugarless gum
- Anticipatory guidance regarding use of
- Syntheticsaliva

Parenteral
- Anticipatory guidance regarding use of
- Probiotics with Lactobacillus

Assess patient & family understanding of recommendations and rationale
- Anticipate need for supplemental nutrition

Dental referral if necessary
- If patient wears dentures, assess for proper fit, areas of irritation, etc.

Systemic opioids may be indicated
- Oral lubricants
- Anticipatory guidance regarding use of
- Syntheticsaliva

Assess for Siccas Syndrome, Sjӧgren's
- Zinc supplements or 0.2% zinc (pembrolizumab, nivolumab)
- Use of dental floss daily
- In
- Immunotherapy to be continued
- Ipilimumab to be withheld for any Grade 2 event (resumption when Grade 0/1)
- Nivolumab to be withheld for first occurrence
- Pembrolizumab (pembrolizumab, nivolumab) or any recurrent Grade 3 event (pembrolizumab, nivolumab)
- Advise ongoing basic oral hygiene

Overall Strategy
(INCLUDING ANTICIPATORY GUIDANCE)

Care Step Pathway - Mucositis & Xerostomia

Nursing Assessment

Grading Toxicity

*Have symptoms worsened?* (Exertion)
- Other reports of dry membranes (e.g., eyes, nose)
- Dry mouth
- Concomitant medications associated with causing
- A history of mouth sores

*Recognize:*
- Parched/peppered, vagina
- Other reports of dry membranes (e.g., eyes, nose)
- Prop of dry mouth when accomplishing mucocutaneous
- Difficult eating
- Mouth sores
- A history of mouth sores

*Listen:*
- Does the patient report?
- Does the patient have thirst?
- Does the patient appear dehydrated?
- Weight loss?
- Dry mouth?
- Difficult eating?
- Does the patient appear unwell?
- Does the patient appear uncommunicable?

*Look:*
- Observe for thrush
- Observe for dry membranes (e.g., eyes, nose)
- Observe the mouth for changes in color (e.g., redness, muting)
- Observe the mouth for changes in texture (e.g., dryness, mucous)
**Management (Including anticipatory guidance)**

**Interventions in at-risk patients**

- Monitor hydration status
- Corticosteroid rinses
  - 0.5% doxepin mouthwash
  - Lesions 15 minutes prior to meals
- 2% viscous lidocaine applied to Gelclair®, Zilactin®
- Anticipation guidance regarding use of pharmacologic agents (as applicable)
  - Encourage soft, bland non-acidic foods
  - Encourage sips of cool water or crushed ice
  - Bicarbonate dissolved in 4 cups of water or bicarbonate rinses if unable to tolerate brushing, advise chlorhexidine gluconate 0.12% or sodium bicarbonate 0.2% orally; tube feeding or total parenteral nutrition indicated; unstimulated saliva <0.1 mL/min orally; tube feeding or total parenteral nutrition indicated; unstimulated saliva 0.1 to 0.2 mL/min; unstimulated saliva ≥0.2 mL/min

**Grades 1 (Mild)**

- Grade 1 (Mild) event persisting >12 weeks
- Grade 1 event persisting >12 weeks
- Grade 1 event persisting >12 weeks
- Grade 1 event persisting >12 weeks
- Grade 1 event persisting >12 weeks

**Grades 2 (Moderate)**

- Grade 2 (Moderate) event persisting >12 weeks
- Grade 2 (Moderate) event persisting >12 weeks
- Grade 2 (Moderate) event persisting >12 weeks
- Grade 2 (Moderate) event persisting >12 weeks
- Grade 2 (Moderate) event persisting >12 weeks

**Grades 3-4 (Severe or Life-Threatening)**

- Grade 3 (Severe) event persisting >12 weeks
- Grade 4 (Potentially Life-Threatening) event persisting >12 weeks
- Grade 5 (Potentially Life-Threatening) event persisting >12 weeks
- Grade 5 (Potentially Life-Threatening) event persisting >12 weeks
- Grade 5 (Potentially Life-Threatening) event persisting >12 weeks

**Definition:** A disorder characterized by reduced salivary flow in the oral region

**Xerostomia (Dry Mouth)**

- Unstimulated saliva <0.1 mL/min
- Unstimulated saliva <0.1 mL/min
- Unstimulated saliva <0.1 mL/min
- Unstimulated saliva <0.1 mL/min
- Unstimulated saliva <0.1 mL/min

**Care Step Pathway**

- Monitor fluid status
- Monitor weight
- Monitor weight
- Monitor weight
- Nutritional counseling

**Mucositis & Xerostomia**

- Assess for other etiology of mucositis or dry mouth: candidiasis; ask patient about new medications (particularly antihistamines), herbs, supplements.

- Evaluate for other etiology of mucositis or dry mouth: candidiasis; ask patient about new medications (particularly antihistamines), herbs, supplements.

- Assess patient & family understanding of toxicity
-自然柠檬
- Sugarless hard candies
- Anticipatory guidance regarding use of pharmacologic agents (as applicable)
  - Assess patient & family understanding of toxicity
  - Oral care
  - Anticipatory guidance regarding use of pharmacologic agents
  - Anticipatory guidance regarding use of pharmacologic agents
  - Anticipatory guidance regarding use of pharmacologic agents
  - Anticipatory guidance regarding use of pharmacologic agents

- Be vigilant for adherence
- Be vigilant for adherence
- Be vigilant for adherence
- Be vigilant for adherence
- Be vigilant for adherence

- Identify barriers to adherence
- Identify barriers to adherence
- Identify barriers to adherence
- Identify barriers to adherence
- Identify barriers to adherence

- Assess for Sicca syndrome, Sjögren's syndrome
- Anticipate hospitalization if unable to tolerate oral solids or liquids
- Anticipate hospitalization if unable to tolerate oral solids or liquids
- Anticipate hospitalization if unable to tolerate oral solids or liquids
- Anticipate hospitalization if unable to tolerate oral solids or liquids

- Encourage vigilant oral hygiene

- Encourage vigilant oral hygiene

- Encourage vigilant oral hygiene

**Overall Strategy**

- Assess for other etiology of mucositis or dry mouth: candidiasis; ask patient about new medications (particularly antihistamines), herbs, supplements.

- Assess for other etiology of mucositis or dry mouth: candidiasis; ask patient about new medications (particularly antihistamines), herbs, supplements.

- Assess patient & family understanding of toxicity
-自然柠檬
- Sugarless hard candies
- Anticipatory guidance regarding use of pharmacologic agents (as applicable)
  - Assess patient & family understanding of toxicity
  - Oral care
  - Anticipatory guidance regarding use of pharmacologic agents (as applicable)
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  - Anticipatory guidance regarding use of pharmacologic agents (as applicable)
  - Anticipatory guidance regarding use of pharmacologic agents (as applicable)

- Be vigilant for adherence
- Be vigilant for adherence
- Be vigilant for adherence
- Be vigilant for adherence
- Be vigilant for adherence

- Identify barriers to adherence
- Identify barriers to adherence
- Identify barriers to adherence
- Identify barriers to adherence
- Identify barriers to adherence
Hepatotoxicity Page 1 of 3

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Nursing Assessment

Care Step Pathway – Hepatotoxicity (Immunotherapy-Induced Inflammation of Liver Tissue)

- Does the patient have any ascites?
- Does the patient appear dehydrated?
- Does the patient appear jaundiced?
- Does the patient appear fatigued or listless?

Look:

Grade 5 (Death)

- Disease progression
- Other potential causes (viral, drug toxicity)
- Syndrome and jaundice
- Symptoms such as abdominal pain, nausea, changes in GI function
- Bilirubin (total/direct)
- ALT/SGPT
- AST/SGOT
- Evolution in LFTs

Recognize:

- Change in weight
- Change in mental status
- Fever
- Bruising or bleeding more easily
- Abdominal pain, especially right upper quadrant pain
- Change in urine color (darker color)
- Change in skin color
- Yellowing
- Change in energy level

Listen:

Grade 4 (Potentially Life-Threatening)

- Bilirubin: >10×ULN
- AST/ALT: >20×ULN

Grade 3 (Severe)

- Bilirubin: >3.0×ULN
- AST/ALT: >5.0×–20.0×ULN

Grade 2 (Moderate)

- Bilirubin: >1.5×–3.0×ULN
- AST/ALT: >3.0×–6.0×ULN

Grade 1 (Mild)

- Bilirubin: >ULN–1.5×ULN
- AST/ALT: >1.5×–3.0×ULN

ULN = upper limit of normal

Bilirubin:     >10×ULN
  Grade 5 (Death)

Bilirubin:     >3.0×ULN
  Grade 4 (Potentially Life-Threatening)

Bilirubin:     >1.5×–3.0×ULN
  Grade 3 (Severe)

Bilirubin:     >ULN–1.5×ULN
  Grade 2 (Moderate)

Bilirubin:     >1.5×–3.0×ULN
  Grade 3 (Severe)

Bilirubin:     >ULN–1.5×ULN
  Grade 2 (Moderate)

Bilirubin:     >3.0×–6.0×ULN
  Grade 1 (Mild)

Bilirubin:     >1.5×–3.0×ULN
  Grade 2 (Moderate)

Bilirubin:     >ULN–1.5×ULN
  Grade 1 (Mild)
Overall Strategy:

**Grade 1 (Mild)**
- Inmunotherapy to be continued
- Daily LFTs
- Remote monitoring
- No change in care plan

**Grade 2 (Moderate)**
- Inmunotherapy to be continued
- Daily LFTs
- Remote monitoring
- Hospital admission
- No change in care plan

**Grade 3 (Severe)**
- Consider stopping immunotherapy
- Daily LFTs
- Close follow-up
- Hospital admission
- Admission for IV steroids
- Hepatology/gastroenterology consult
- Anti-acid therapy daily as gastric ulcer prevention while on steroids
- Long-term high-dose steroids: Be alert to recurring symptoms as steroids taper down & report them (taper may need to be adjusted)
- Review steroid medication side effects: mood changes (anger, reactive, hyperaware, euphoric, mania), increased appetite, interrupted sleep, oral thrush, fluid retention
- Close follow-up in person or by phone, based on individual need & symptomatology
- Taper should consider patient’s current symptom profile
- *Steroid taper instructions/calendar as a guide but not an absolute

Grade LFTs and any other accompanying symptoms

- Early identification and evaluation of patient symptoms
- Review LFT results prior to administration of immunotherapy

Nursing Implementation:

- 4 weeks over ≥ 6 weeks
- If LFTs normalized and symptoms resolved, consider resuming treatment
- Consider liver biopsy
- If LFTs normalized and symptoms resolved, steroids* to be tapered
- Steroids* to be tapered over ≥ 6 weeks (pembrolizumab, nivolumab), ≥ 12 weeks (ipilimumab) or ≥ 6 weeks (nivolumab)
- Grade 2 events lasting 1–6 weeks (pembrolizumab, nivolumab, ipilimumab) or any Grade 3 event, and nivolumab or pembrolizumab for any recurrent Grade 3 event
- Ipilimumab to be discontinued of any Grade 3 event
- Nivolumab to be withheld for first occurrence
- Admission for IV steroids

---

**Hepatotoxicity**

- Bilirubin (>3.0×ULN)
- AST/ALT (>3.0×ULN)
- AST/ALT: >20×ULN
- Bilirubin: >1.5×–3.0×ULN
- Bilirubin: >10×ULN

- Mild
- Moderate
- Severe
- Potentially Life Threatening

- Liver function tests
- Consider stopping immunotherapy

---

**Hepatitis**

- Inflammation of liver tissue
- Increased sweating?
- Change in mental status?
- Abdominal pain: specifically, right upper quadrant pain?
- Change in skin color? Yellowing?
- Change in urine color (darker/tea colored)?
- Change in stool color (paler)?
- Bruising or bleeding more easily?
- Increased spontaneous diaphoresis
- Increased thirst
- Nausea and vomiting
- Fever
- Change in LFTs
- Fever
- Change in LFTs
- Change in LFTs

**Infliximab infusions are not recommended due to potential hepatotoxic effects**

Inmunotherapy infusions are not recommended due to potential hepatotoxic effects

---

**Management (including anticipatory guidance)**

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**RED FLAGS:**

- Avoid alcohol/acetaminophen or other hepatotoxins
- Consider additional antiviral and antifungal coverage
- Severe abdominal pain, ascites, somnolence, jaundice, mental status changes
- Grade LFTs to be checked and results reviewed prior to each dose of immunotherapy
Severe abdominal pain, ascites, somnolence, jaundice, mental status changes

RED FLAGS:

- Severe abdominal pain, ascites, somnolence, jaundice, mental status changes
- Early intervention with lab work and office visit if hepatotoxicity is suspected
- Review LFT results prior to administration of immunotherapy
- Early identification and evaluation of patient symptoms
- Nursing Implementation:

Nursing Implementation:

Grade LFTs and any other accompanying symptoms

Care Step Pathway

- Early intervention with lab work and office visit if hepatotoxicity is suspected
- Early identification and evaluation of patient symptoms
- Review LFT results prior to administration of immunotherapy

AST/ALT: >20×ULN
AST/ALT: >5.0×–20.0×ULN
AST/ALT: >3.0×–5.0×ULN
AST/ALT: >ULN–3.0×ULN

Pyruvic transaminase; ULN = upper limit of normal

ALT = aspartate transaminase; AST = aspartate aminotransferase; GI = gastrointestinal; LFT = liver function test; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic

AL = alanine aminotransferase; AST = aspartate aminotransferase; GI = gastrointestinal; LFT = liver function test; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic

- Severe abdominal pain, ascites, somnolence, jaundice, mental status changes

RED FLAGS:

- Consider additional antiviral and antifungal coverage
- Consider antimicrobial prophylaxis (sulfamethoxazole/trimethoprim double dose M/W/F; single dose if used daily) or alternative if sulfa-allergic (e.g., atovaquone [Mepron®] 1500 mg po daily)
- Long-term high-dose steroids:
  - Tapers should consider patient's current symptom profile
  - Early intervention with lab work and office visit if hepatotoxicity is suspected
  - Early identification and evaluation of patient symptoms
  - Review LFT results prior to administration of immunotherapy
  - Nursing Implementation:

Nursing Implementation:

Grade LFTs and any other accompanying symptoms

Care Step Pathway

- Early intervention with lab work and office visit if hepatotoxicity is suspected
- Early identification and evaluation of patient symptoms
- Review LFT results prior to administration of immunotherapy

AST/ALT: >20×ULN
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- Long-term high-dose steroids:
  - Tapers should consider patient's current symptom profile
  - Early intervention with lab work and office visit if hepatotoxicity is suspected
  - Early identification and evaluation of patient symptoms
  - Review LFT results prior to administration of immunotherapy
  - Nursing Implementation:

Nursing Implementation:

Grade LFTs and any other accompanying symptoms

Care Step Pathway

- Early intervention with lab work and office visit if hepatotoxicity is suspected
- Early identification and evaluation of patient symptoms
- Review LFT results prior to administration of immunotherapy

AST/ALT: >20×ULN
AST/ALT: >5.0×–20.0×ULN
AST/ALT: >3.0×–5.0×ULN
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RED FLAGS:

- Consider additional antiviral and antifungal coverage
- Consider antimicrobial prophylaxis (sulfamethoxazole/trimethoprim double dose M/W/F; single dose if used daily) or alternative if sulfa-allergic (e.g., atovaquone [Mepron®] 1500 mg po daily)
- Long-term high-dose steroids:
  - Tapers should consider patient's current symptom profile
  - Early intervention with lab work and office visit if hepatotoxicity is suspected
  - Early identification and evaluation of patient symptoms
  - Review LFT results prior to administration of immunotherapy
  - Nursing Implementation:

Nursing Implementation:

Grade LFTs and any other accompanying symptoms

Care Step Pathway

- Early intervention with lab work and office visit if hepatotoxicity is suspected
- Early identification and evaluation of patient symptoms
- Review LFT results prior to administration of immunotherapy

AST/ALT: >20×ULN
AST/ALT: >5.0×–20.0×ULN
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- Severe abdominal pain, ascites, somnolence, jaundice, mental status changes

RED FLAGS:

- Consider additional antiviral and antifungal coverage
- Consider antimicrobial prophylaxis (sulfamethoxazole/trimethoprim double dose M/W/F; single dose if used daily) or alternative if sulfa-allergic (e.g., atovaquone [Mepron®] 1500 mg po daily)
- Long-term high-dose steroids:
  - Tapers should consider patient's current symptom profile
  - Early intervention with lab work and office visit if hepatotoxicity is suspected
  - Early identification and evaluation of patient symptoms
  - Review LFT results prior to administration of immunotherapy
  - Nursing Implementation:

Nursing Implementation:

Grade LFTs and any other accompanying symptoms

Care Step Pathway

- Early intervention with lab work and office visit if hepatotoxicity is suspected
- Early identification and evaluation of patient symptoms
- Review LFT results prior to administration of immunotherapy

AST/ALT: >20×ULN
AST/ALT: >5.0×–20.0×ULN
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Hypophysitis

Nursing Assessment

Care Step Pathway – Hypophysitis (Inflammation of the Pituitary Gland)

Look:
- Does the patient appear fatigued?
- Does the patient look listless?
- Does the patient look ill?
- Does the patient look uncomfortable?

Grading Toxicity (Overall)

Listen:
- Does the patient report:
  - Change in energy?
  - Headache?
  - Dizziness?
  - Nausea/vomiting?
  - Altered mental status?
  - Visual disturbances?
  - Fever?

Recognize:
- Low levels of hormones produced by pituitary gland (ACTH, TSH, FSH, LH, prolactin)
- Brain MRI with pituitary cuts: enhancement and swelling of the pituitary gland
- DDX adrenal Insufficiency: low cortisol and high ACTH
- DDX primary hypothyroidism: low free T4 and high TSH

Management

Overall Strategy:
- Ipilimumab to be withheld for any symptomatic hypophysitis and discontinued for symptomatic reactions persisting ≥6 weeks or for inability to reduce steroid dose to ≤7.5 mg prednisone or equivalent per day
- Nivolumab to be withheld for Grade 2/3 hypophysitis and discontinued for Grade 4 hypophysitis. Pembrolizumab to be withheld for Grade 2 hypophysitis and withheld or discontinued for Grade 3/4 hypophysitis.
- 1 mg/kg methylprednisolone (or equivalent) IV to be given daily if given during acute phase, may reverse inflammatory process
- To be followed with prednisone 1–2 mg/kg daily with gradual tapering over at least 4 weeks
- Low levels of hormones produced by pituitary gland

- Long-term supplementation of affected hormones is often required
- Secondary hypothyroidism requiring levothyroxine replacement
- Secondary hypothyroidism requiring levothyroxine replacement
- Secondary hypothyroidism requiring levothyroxine replacement
- Secondary hypothyroidism requiring levothyroxine replacement

Grade 1 (Mild)
- Asymptomatic or mild symptoms; clinical or diagnostic observation only (headache, fatigue)

Grade 2 (Moderate)
- Moderate symptoms; limiting age-appropriate instrumental ADLs (headache, fatigue)

Grade 3 (Severe)
- Severe or medically significant symptoms; limiting self-care ADLs (sepsis, severe ataxia)

Grade 4 (Potentially Life-Threatening)
- Urgent intervention required (sepsis, severe ataxia)

Grade 5 (Death)

Nursing Implementation:
- ACTH and thyroid panel should be checked at baseline and prior to each dose of ipilimumab
- Ensure that MRI is ordered with pituitary cuts or via pituitary protocol
- Anticipate treatment with corticosteroid and immunotherapy hold
- Review proper administration of steroid
  - Take with food
  - Take in AM
- Educate patient regarding possibility of permanent loss of organ function (pituitary; possibly others if involved [thyroid, adrenal glands])
- Sick-day instructions, vaccinations, etc
- Steroid taper instructions/calendar as a guide but not an absolute
- Tapers should consider patient’s current symptom profile
- Close follow-up in person or by phone, based on individual need & symptomatology
- Anti-acid therapy daily as gastric ulcer prevention while on steroids
- Review steroid medication side effects: mood changes (anger, reactive, hyperaware, euphoric, mania), increased appetite, interrupted sleep, oral thrush, fluid retention
- Be alert to recurring symptoms as steroids taper down & report them (taper may need to be adjusted)
- Long-term high-dose steroids:
  - Consider antimicrobial prophylaxis (sulfamethoxazole/trimethoprim double dose M/W/F; single dose if used daily) or alternative if sulfa-allergic (e.g., atovaquone [Mepron®] 1500 mg po daily)
  - Consider additional antiviral and antifungal coverage
  - Avoid alcohol/acetaminophen or other hepatotoxins

ACTH = adrenocorticotropic hormone; ADLs = activities of daily living; DDX = differential diagnosis; FSH = follicle-stimulating hormone; GH = growth hormone; LH = luteinizing hormone; MRI = magnetic resonance imaging; TSH = thyroid stimulating hormone.
Nursing Assessment

Care Step Pathway – Hypophysitis

- Inflammation of the pituitary gland

Look:
- Does the patient appear fatigued?
- Does the patient look listless?
- Does the patient look ill?
- Does the patient look uncomfortable?

Listen:
- Does the patient report:
  - Change in energy?
  - Headache?
  - Dizziness?
  - Nausea/vomiting?
  - Altered mental status?
  - Visual disturbances?
  - Fever?

Recognize:
- Low levels of hormones produced by the pituitary gland (ACTH, TSH, FSH, LH, GH, prolactin)
- Brain MRI with pituitary cuts: enhancement and swelling of the pituitary gland.
- DDX adrenal Insufficiency: low cortisol and high ACTH
- DDX primary hypothyroidism: low free T4 and high TSH

Management

Overall Strategy:
- Ipilimumab to be withheld for any symptomatic hypophysitis and discontinued for symptomatic reactions persisting ≥ 6 weeks or for inability to reduce steroid dose to ≤ 7.5 mg prednisone or equivalent per day
- Nivolumab to be withheld for Grade 2/3 hypophysitis and discontinued for Grade 4 hypophysitis. Pembrolizumab to be withheld for Grade 2 hypophysitis and withheld or discontinued for Grade 3/4 hypophysitis
- 1mg/kg methylprednisolone (or equivalent) IV to be given daily
  - If given during acute phase, may reverse inflammatory process
- To be followed with prednisone 1-2mg/kg daily with gradual tapering over at least 4 weeks
- Long-term supplementation of affected hormones is often required
  - Secondary hypothyroidism requiring levothyroxine replacement
  - Secondary hypoadrenalism requiring replacement hydrocortisone
    - Typical dose: 20 mg qAM and 10 mg qPM
  - Assess risk of opportunistic infection based on duration of steroid taper (and consider prophylaxis if needed)
  - Collaborative management approach with endocrinology (particularly if permanent loss of organ function)

Grade 1 (Mild)
- Asymptomatic or mild symptoms; clinical or diagnostic observation only (headache, fatigue)

Grade 2 (Moderate)
- Moderate symptoms; limiting age-appropriate instrumental ADLs (headache, fatigue)

Grade 3 (Severe)
- Severe or medically significant symptoms; limiting self-care ADL (sepsis, severe ataxia)

Grade 4 (Potentially Life-Threatening)
- Urgent intervention required (sepsis, severe ataxia)

Grade 5 (Death)

Nursing Implementation:
- ACTH and thyroid panel should be checked at baseline and prior to each dose if immunomodulation
- Steroid taper instructions/calendar as a guide but not an absolute
- Tapers should consider patient's current symptom profile
- Close follow-up in person or by phone, based on individual need & symptomatology
- Anti-acid therapy daily as gastric ulcer prevention while on steroids
- Review steroid medication side effects, mood changes (anger, irritability, sleep disturbances), increased appetite, infections, fluid retention, oral thrush

RED FLAGS:
- Symptom of adrenal insufficiency
- Red flag dose steroids
- Be alert to mounting symptoms as steroids are reduced (report down x report them upper may need to be addressed)
- Review steroid medication side effects, mood changes (anger, irritability, sleep disturbances, increased appetite, infections, fluid retention, oral thrush)
- Close follow-up in person or phone, based on individual need & symptomatology
- Take with food
- Take in AM

ACTH = adrenocorticotropic hormone; ADLs = activities of daily living; DDX = differential diagnosis; FSH = follicle-stimulating hormone; GH = growth hormone; LH = luteinizing hormone; MRI = magnetic resonance imaging; TSH = thyroid stimulating hormone.
### Thyroiditis

**Nursing Assessment**

#### Look:
- Does the patient appear unwell?
- Changes in weight since last visit
- Does the patient appear fatigued?
- Changes in hair texture/thickness?
- Changes in appetite/weight?
- Hot or cold intolerance?
- Change in energy, mood, or behavior?
- Palpitations?
- Increased fatigue?
- Bowel-related changes?
- o Constipation/diarrhea
- Skin-related changes?
- o Dry/oily

#### Type of Thyroid Abnormality

<table>
<thead>
<tr>
<th>TSH (mIU/L)</th>
<th>Free T4 or T3 (normal or low)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5, &lt;10</td>
<td>normal or high free T4 or T3</td>
<td>Primary hypothyroidism</td>
</tr>
<tr>
<td>&gt;10</td>
<td>normal or low free T4 &amp; T3</td>
<td>Secondary hypothyroidism</td>
</tr>
</tbody>
</table>

**Management**

- **TSH >5, <10 mIU/L with normal free T4, T3**
  - Repeat TFTs in 4–6 weeks
- **TSH >10 mIU/L with normal or low free T4 & T3**
  - Begin thyroid replacement if symptomatic
  - May consider repeating levels in 2-4 weeks if asymptomatic
  - Levothyroxine dose 1.6 mcg per pound or 75–100 mcg daily
  - Repeat TSH in 4–6 weeks and titrate dose to reference range
- **TSH low or <0.01 mIU/L with high free T4 or T3**
  - Consider radioactive iodine therapy or methimazole treatment
  - Consider use of beta blockers for symptomatic patients (e.g., for tachycardia or murmur)
- **TSH low or <0.01 mIU/L with normal or high free T3 or T4**
  - Acute thyroiditis
  - Rarely Graves'-like disease
- **TSH >5, <10 mIU/L with normal free T4, T3**
  - Subclinical hypothyroidism
- **TSH >10 mIU/L with normal or low free T4 & T3**
  - Primary hypothyroidism
- **TSH low or <0.01 mIU/L with high free T4 or T3**
  - Hyperthyroidism
  - Consider measuring anti-thyroid antibodies and/or TSH-receptor autoantibodies (TRAB) to establish autoimmune etiology
  - If patient has not received IV iodinated contrast within 2 months, can consider a diagnostic thyroid uptake & scan
  - Acute thyroiditis usually resolves or progresses to hypothyroidism; thus, can repeat TFTs in 4–6 weeks
  - If TRAB high, obtain a thyroid uptake scan & refer to endocrinology
  - Short period of 1 mg/kg prednisone or equivalent may be helpful in acute thyroiditis
  - Consider use of beta blockers and immunotherapy holds for symptomatic patients (e.g., beta blockers for tachycardia or murmur and immunotherapy holds for patients who have acute thyroiditis threatening an airway). Therapy is often restarted when symptoms are mild/tolerable

**Nursing Implementation**

- Educate patient that hypothyroidism is generally not reversible
- Assess medication compliance with oral thyroid replacement or suppression
- History of thyroid disorders does not increase or decrease risk of incidence
- Consider collaborative management with endocrinologist, especially if the patient is hyperthyroid, particularly if a thyroid scan is needed

**RED FLAGS:**
- Swelling of thyroid gland causing compromised airway

---

*DDX = differential diagnosis; PD-1 = programmed cell death protein 1; TFT = thyroid function test; TSH = thyroid stimulating hormone*
Thyroiditis

Care Step Pathway – Thyroiditis

Nursing Assessment

Look:
- Does the patient appear unwell?
- Changes in weight since last visit: Appear heavier? Thinner?
- Changes in hair texture/thickness?
- Appearing hot/cold?
- Does the patient look fatigued?

Listen:
- Appetite/weight changes?
- Hot or cold intolerance?
- Change in energy, mood, or behavior?
- Palpitations?
- Increased fatigue?
- Bowel-related changes: Constipation/diarrhea
- Skin-related changes: Dry/oily

Recognize:
- Ensure that patient undergoes thyroid function tests prior to first dose, every 12 weeks while on PD-1 therapy and q3 weeks with ipilimumab.
- High TSH with low free T4 consistent with primary hypothyroidism.
- DDX: secondary hypothyroidism due to hypophysitis, low TSH and low free T4.
- Occasionally thyroiditis with transient hyperthyroidism (low TSH and high free T4) may be followed by more longstanding hypothyroidism (high TSH and low free T4).
- Other immune-related toxicity?
- Prior thyroid dysfunction?

Management

TSH > 5, < 10 mIU/L with normal free T4, T3:
- Repeat TFTs in 4–6 weeks.

TSH > 10 with normal or low free T4 & T3:
- Begin thyroid replacement if symptomatic.
- May consider repeating levels in 2–4 weeks if asymptomatic.
- Levothyroxine dose 1.6 mcg per weight (kg) or 75–100 mcg daily.
- Repeat TSH in 4–6 weeks and titrate dose to reference range.

TSH low or < 0.01 mIU/L with high free T4 or T3:
- Consider radioactive iodine therapy or methimazole treatment.
- Consider use of beta blockers.

TSH low or < 0.01 mIU/L with normal or high free T3 or T4:
- Acute thyroiditis.
- Rarely Graves’-like disease.

TSH > 5, < 10 mIU/L with normal free T4, T3:
- Subclinical hypothyroidism.

TSH > 10 mIU/L with normal or low free T4 & T3:
- Primary hypothyroidism.

TSH low or < 0.01 mIU/L with high free T4 or T3:
- Hyperthyroidism.
- Consider measuring anti-thyroid antibodies and/or TSH-receptor autoantibodies (TRAB) to establish autoimmune etiology.
- If patient has not received IV iodinated contrast within 2 months, can consider a diagnostic thyroid uptake & scan.
- Acute thyroiditis usually resolves or progresses to hypothyroidism; thus, can repeat TFTs in 4–6 weeks.
- If TRAB high, obtain a thyroid uptake & scan & refer to endocrinology.
- Short period of 1 mg/kg prednisone or equivalent may be helpful in acute thyroiditis.
- Consider use of beta blockers and immunotherapy holds for symptomatic patients (e.g., beta blockers for tachycardia/murmur and immunotherapy holds for patients who have thyroid storm/hyperthyroidism).

Nursing Implementation:

- Educate patient that hypothyroidism is generally not reversible.
- Assess medication compliance with oral thyroid replacement or suppression.
- History of thyroid disorders does not increase or decrease risk of incidence.
- Educate patient that hypothyroidism is generally not reversible.

RED FLAGS:
- Swelling of thyroid gland causing compromised airway.
- Other immune-related toxicity.

DDX = differential diagnosis; PD-1 = programmed cell death protein 1; TFT = thyroid function test; TSH = thyroid stimulating hormone.
Care Step Pathway - Type 1 Diabetes Mellitus (Immune destruction of beta cells in pancreas)

Care Step 1: Nursing Assessment

Look:
- Does the patient appear fatigued?
- Does the patient appear dehydrated?
- Does the breath have a sweet/fruity smell?
- Is the patient tachycardic?

Grading Toxicity (Based on Fasting Glucose)

Grade 1 (Mild):
Fasting glucose value > 160 mg/dL

Grade 2 (Moderate):
Fasting glucose value > 250 – 500 mg/dL

Grade 3 (Severe):
Fasting glucose value > 250–500 mg/dL, hospitalization indicated

Grade 4 (Potentially Life-Threatening):
Fasting glucose value > 500 mg/dL, life-threatening consequences

Grade 5 (Death):
Fasting glucose value > 750 mg/dL

Grading Toxicity (Based on Fasting Glucose)

Recognize:
- Other immune-related toxicity
- Serum glucose levels
- Symptoms of diabetes

Nursing Implementation:
- Endocrine consult
- Hydration
- Insulin therapy
- Immunotherapy may be withheld until blood glucose is regulated
- Immunotherapies may be withheld until blood glucose is regulated
- Other immune-related AEs, including those of endocrine origin

Overall Strategy:
- Insulin therapy
- Hydration
- Endocrine consult
- Other immune-related AEs
- Serum glucose levels
- Symptoms of diabetes

DM = diabetes mellitus; ULN = upper limit of normal

DM = diabetes mellitus; ULN = upper limit of normal
**Pneumonitis**

**Grading Toxicity**

<table>
<thead>
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**Definition:** A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma.

**Interleukin-2**

- **Definition:** A lymphokine produced by helper T cells.
- **Function:** Activates cytotoxic T cells and natural killer cells.
- **Side Effects:** Hypotension, chest pain, dyspnea, facial edema.

**Pneumonitis**

- **Definition:** Inflammation of the lung tissue.
- **Symptoms:** Cough, dyspnea, chest pain, fever.

**Nursing Assessment**

**Look:**
- Does the patient appear to be in respiratory distress?
- Does the patient appear short of breath?
- Does the patient have difficulty walking to the exam?

**Listen:**
- Does the patient notice a new cough? Or a change in breathing?
- Does the patient note any change in breathing?

**Recognize:**
- Has the patient experienced other immune-related adverse effects?
- Has the patient experienced other respiratory symptoms (e.g., asthma, COPD, congestive heart failure)?

**Assess for other etiologies:**
- Infection
- Pulmonary embolism
- Progressive lung metastases
- Lung disease

**Identify barriers to adherence:**
- Comprehension of treatment plan
- Compliance with medication
- Physical activity

**Early intervention to maintain or improve physical function and impact on QOL**

**Prevention**

**Grading Toxicity**

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**Definition:** A disorder characterized by decrease in the level of oxygen to the body.

**Hypoxia**

- **Definition:** Decreased oxygen saturation.
- **Severity:**
  - Grade 1: Mild
  - Grade 2: Moderate
  - Grade 3: Severe
  - Grade 4: Potentially Life-Threatening
  - Grade 5: Life-Threatening

**Recognize:**
- Decreased oxygen saturation
- Decreased oxygen saturation with activity

**Listen:**
- Does the patient appear short of breath?
- Does the patient notice a new cough?

**Look:**
- Does the patient appear uncomfortable?
- Does the patient appear to be in respiratory distress?

**Assess for other etiologies:**
- Infection
- Pulmonary embolism
- Progressive lung metastases
- Lung disease

**Identify barriers to adherence:**
- Comprehension of treatment plan
- Compliance with medication
- Physical activity

**Early intervention to maintain or improve physical function and impact on QOL**

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**Nursing Assessment**

**Look:**
- Does the patient appear to be in respiratory distress?
- Does the patient appear short of breath?
- Does the patient have difficulty walking to the exam?

**Listen:**
- Does the patient notice a new cough? Or a change in breathing?
- Does the patient note any change in breathing?

**Recognize:**
- Has the patient experienced other immune-related adverse effects?
- Has the patient experienced other respiratory symptoms (e.g., asthma, COPD, congestive heart failure)?

**Assess for other etiologies:**
- Infection
- Pulmonary embolism
- Progressive lung metastases
- Lung disease
**Risk of pneumonitis is greater in patients receiving combination immunotherapy regimens**

- Risk of mortality if pneumonitis treatment is delayed

**RED FLAGS:**

- Educate patients and family about the rationale for discontinuation of immunotherapy in patients who do develop moderate or severe pneumonitis
- Anticipate that the standard recommendations to manage pneumonitis are right (1–3 mg/kg/day) and present with 3–5 cm consolidations is likely to resolve immediately
- Educate patients that new pulmonary symptoms should be reported immediately
- Early high-risk medications (e.g., statins, COPD) and those with cardiac pulmonary symptoms prior to initiating immunotherapy

**Nursing Implementation:**

- Identify barriers to adherence
- Anticipate that bronchoscopy may be completed. IV corticosteroids may be administered
- Identify barriers to adherence
- Anticipate the use of additional immunosuppressive agents if symptoms do not improve in 48–72 hours
- Consider symptoms limiting ADLs; oxygen indicated
- Assess patient & family understanding of toxicity and rationale for treatment discontinuation
- Patient will likely need to be admitted to the hospital for further management and testing (q 2–4 weeks, as needed)
- Symptomatic; medical intervention indicated (tracheostomy, intubation)
- Grade 1 (Mild)
- Grade 2 (Moderate)
- Grade 3 (Severe)
- Grade 4 (Severe or Life Threatening)
- Grade 5 (Potentially Life Threatening)

**Management**

- Early treatment with high-dose IV corticosteroids (e.g., prednisone 1–2 mg/kg/day; equivalent)
- Symptomatic management with bronchodilators and oxygen
- Increase dose of immunosuppressive or immunosuppressive + corticosteroid
- If disease does not improve within 48 hours, consult with pulmonologist and cardiology
- Assess for other etiologies such as infection, primary pulmonary embolism, progressive lung metastases, or lung disease

**Overall Strategy:**

- Discontinue immunotherapy for Grade 3/4
- Immunotherapy to continue
- Patient will likely need to be admitted to hospital for further management and testing (q 2–4 weeks, as needed)
- Symptomatic; medical intervention indicated (tracheostomy, intubation)
- Grade 1 (Mild)
- No known interventions

**Prevention**

- Early intervention to monitor or improve physical function and impact on QOL
- Assess for other etiologies such as infection, primary pulmonary embolism, progressive lung metastases, or lung disease
- Early high-risk medications (e.g., statins, COPD) and those with cardiac pulmonary symptoms prior to initiating immunotherapy

**Pneumonitis**

- A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma
- Definition: A disorder characterized by decrease in the level of oxygen to the body
- Acute hypoxia
- Hypoxia
- Pneumonitis

**ADL = activities of daily living; COPD = chronic obstructive pulmonary disease**
Arthralgias and Arthritis

**Nursing Assessment**

**Care Step Pathway - Arthralgias and Arthritis**

**Risk of Fall due to Mobility Issues**

**Red Flags:**
- Anticipate that the steroid requirements to manage arthralgias can be much higher (i.e., up to 1.5 mg/kg/day) than typically required to manage "classic" inflammatory arthritis
- Educate patients that arthralgias and arthritis are the most commonly reported rheumatic and musculoskeletal irAEs with checkpoint inhibitors
- Identify high-risk individuals and those with underlying autoimmune dysfunction
- Identify barriers to adherence, specifically compliance
- Assess patient & family understanding of toxicity and rationale for treatment discontinuation

**Agents NOT advised**
- Rituximab
- Anti B-cell agents (CD-20 blocking)

**escalate to next level of therapy**
- 6 weeks, escalate to next level of therapy
- 6 – 12 weeks, escalate to next level of therapy

**Assessment**
- Is the patient having trouble getting up and down?
- Does the patient appear unwell?
- Does the patient appear uncomfortable?
- Does the patient have pain in the feet?
- Does the patient have pain in the hands?
- Does the patient have pain in the wrist?
- Does the patient have pain in the fingers?
- Does the patient have pain in the back?
- Does the patient have pain in the neck?
- Does the patient have pain in the hip?
- Does the patient have pain in the shoulder?
- Does the patient have pain in the knee?
- Does the patient have pain in the elbow?
- Does the patient have pain in the ankle?
- Does the patient have pain in the foot?
- Does the patient have pain in the hand?
- Does the patient have pain in the finger?
- Does the patient have pain in the upper back?
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- Does the patient have pain in the spine?
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- Does the patient have pain in the lower back?
- Does the patient have pain in the spine?
- Does the patient have pain in the head?
- Does the patient have pain in the neck?
- Does the patient have pain in the shoulder?
- Does the patient have pain in the hip?
Behavioral interventions including physical activity, exercise, mindfulness, and relaxation strategies may help. Physical activity, which includes walking, swimming, and cycling, can improve physical function and quality of life. Exercise programs specifically designed for arthritis, such as aqua aerobics or Tai Chi, may also be helpful. Mindfulness-based stress reduction, yoga, and tai chi can help manage pain and improve overall well-being. Sleep hygiene and sleep promotion strategies can improve quality of life. Massage therapy, acupuncture, and other complementary therapies may also provide relief. It is important to work with healthcare providers to develop a comprehensive plan that addresses the individual needs and preferences of the patient.

Assessment and Management

Assessment

- Symptom severity and duration
- Physical examination: range of motion, joint tenderness, swelling, and muscle strength
- Laboratory tests: CRP, ESR, ANA, RF, anti-CCP, anti-cyclic citrullinated peptide (anti-CCP), anti-nuclear antibody (ANA)
- Imaging studies: X-rays, MRI, ultrasound

Management

- Non-pharmacological interventions
  - Physical therapy
  - Occupational therapy
  - Educational interventions
- Pharmacological interventions
  - Non-steroidal anti-inflammatory drugs (NSAIDs)
  - Disease-modifying antirheumatic drugs (DMARDs)
  - Biologic agents
  - Corticosteroids

- Monitoring and follow-up
  - Regular assessments of symptom control and functional status
  - Adjustments to treatment based on response and side effects

Prevention

- Regular physical activity
- Healthy diet
- Weight management
- Stress management
- Good sleep hygiene

Overall Strategies

- Early intervention to minimize the impact on physical function and quality of life
- Regular assessment and titration of medications
- Patient education and involvement in decision-making
RISK OF FALL DUE TO MOBILITY ISSUE

RED FLAGS:

- Anticipate falls due to mobility issues
- Recognize:
  - Does the patient appear unwell?
  - Is there a pre-existing autoimmune dysfunction?
  - Is there a history of prior orthopedic injury, DJD, OA, RA?
  - Are symptoms increasing the patient's risk for fall? Other safety issues?
  - Are symptoms limiting ADLs?
  - Associated symptoms?

Nursing Implications:

- Educate patients that symptoms can persist beyond treatment completion due to the mechanism of checkpoint inhibitors.
- Anticipate that the steroid requirements to manage arthralgias can be much higher (i.e., up to 1.5 mg/kg/day) than typically required to manage “classic” inflammatory arthritis.
- Arthralgia-like symptoms range from mild (managed well with NSAIDs) to severe and erosive (requiring multiple immunosuppressant medications).
- Educate patients that arthritis and arthralgia are the most commonly reported neurologic and musculoskeletal issues with checkpoint inhibitors.
- Identify high-risk individuals and those with underlying autoimmune dysfunction.

Grading Toxicity

- Grade 1 (Mild)
  - Fatigue (new or worsening)
  - Sore throat
  - Headache
  - Nausea
  - Vomiting

- Grade 2 (Moderate)
  - Grade 1 (Mild) plus)
  - Diarrhea
  - Increased alkaline phosphatase
  - Increased liver enzymes
  - Increased creatinine

- Grade 3 (Severe)
  - Grade 2 (Moderate) plus)
  - Moderate pain associated with signs of inflammation, erythema, or joint swelling
  - Fatigue (new or worsening)
  - Sore throat

- Grade 4 (Potentially Life Threatening)
  - Grade 3 (Severe) plus)
  - Severe pain associated with signs of inflammation, erythema, or joint swelling

- Grade 5 (Death)
  - Grade 4 (Potentially Life Threatening) plus)

Definition: A disorder characterized by inflammation involving a joint

Definition: A disorder characterized by a sensation of marked discomfort in a joint

Ankylosing spondylitis
- Type A ankle pain
- Type B articular pain

Spondyloarthritis
- Type A ankle pain
- Type B articular pain

Hodgkin lymphoma
- Type A ankle pain
- Type B articular pain

Malignant pleural effusion
- Type A ankle pain
- Type B articular pain

Non-small cell lung cancer
- Type A ankle pain
- Type B articular pain

Definition: A disorder characterized by a sensation of marked discomfort in a joint
Care Step Pathway – Neuropathy (motor or sensory nerve impairment or damage)

Nursing Assessment

Look:
- Does the patient appear weak?
- Does the patient appear uncomfortable?
- Altered ambulation or general movement?
- If muscular weakness is present, any respiratory difficulties apparent?

Listen:
- Does the patient report weakness (unilateral or bilateral)?
- Does the patient report new or worsened pain, numbness, or tingling?
- Does the patient report difficulty walking or holding items?

Recognize:
- Motor deficits
- Sensory deficits
- Mental status changes
- Paresthesias
- Laboratory values

Grading of Neuropathy:

Grade 1 (Mild)
- Peripheral Motor: Asymptomatic; clinical or diagnostic observations only
- Peripheral Sensory: Asymptomatic; loss of deep tendon reflexes or paresthesia

Grade 2 (Moderate)
- Peripheral Motor: Moderate symptoms; limiting ADLs
- Peripheral Sensory: Moderate symptoms; limiting ADLs

Grade 3 (Severe)
- Peripheral Motor: Severe symptoms; limiting self-care ADLs; requires assistive devices
- Peripheral Sensory: Severe symptoms; limiting self-care ADLs

Grade 4 (Potentially Life-Threatening)
- Peripheral Motor: Life-threatening; urgent intervention indicated
- Peripheral Sensory: Life-threatening; urgent intervention indicated

Grade 5 (Death)
- Peripheral Motor: Life-threatening; urgent intervention indicated
- Peripheral Sensitivity: Life-threatening; urgent intervention indicated

Management

Overall Strategy:
- Rule out infectious, non-infectious, disease-related etiologies
- High-dose steroids (1–2 mg/kg/day prednisone or equivalent) to be used
- Ipilimumab to be withheld for Grade 2 event, nivolumab for first occurrence of Grade 3 event, and pembrolizumab based on disease severity
- Ipilimumab to be discontinued for Grade 2 events persisting ≥ 6 weeks or inability to reduce steroid dose to ≤ 7.5 mg prednisone or equivalent per day
- Pembrolizumab or nivolumab to be discontinued for Grade 3/4 events that recur, persist ≥ 12 weeks, or inability to reduce steroid dose to ≤ 10 mg prednisone or equivalent per day
- Metastases to spinal cord
- Other metastases that may cause symptoms
- Neurology consult
- Consideration of electromyelogram and nerve conduction tests
- Immune globulin infusions
- Plasmapheresis
- Taper steroids slowly over at least 4 weeks once symptoms improve
- Supportive medications for symptomatic management
- Nutritional support
- Early identification and evaluation of patient symptoms
- Early intervention with lab work and office visit if neuropathy symptoms suspected

Red Flags:
- Guillain–Barré syndrome
- Myasthenia gravis

Steroid taper instructions/calendar as a guide but not an absolute
- Taper should consider patient’s current symptom profile
- Close follow-up in person or by phone, based on individual need and symptomatology
- Anti-acid therapy daily as gastric ulcer prevention while on steroids
- Review steroid medication side effects: mood changes (anger, reactive, hyperaware, euphoric, mania), increased appetite, interrupted sleep, oral thrush, fluid retention
- Be alert to recurring symptoms as steroids taper down & report them (taper may need to be adjusted)

Long-term high-dose steroids:
- Consider antimicrobial prophylaxis (sulfamethoxazole/trimethoprim double dose M/W/F; single dose if used daily) or alternative if sulfa-allergic (e.g., atovaquone [Mepron®] 1500 mg po daily)
- Consider additional antiviral and antifungal coverage
- Avoid alcohol/acetaminophen or other hepatoxins

Care Step Pathway – Neuropathy (motor or sensory nerve impairment or damage)
Neuropathy Page 2 of 2

**Nursing Implications:**

- Early intervention with lab work and office visit if neuropathy symptoms suspected
- Early identification and evaluation of gentler symptoms
- Comply baseline assessment grade 4 document neuropathy and etiology (diabetic, medication, vascular, chemotherapy)

**Red Flags:**

- Guillain–Barré syndrome

**Grade 1 (Mild)**

- Peripheral Motor: Asymptomatic; clinical or diagnostic observations only
- No intervention indicated

- Peripheral Sensory: Asymptomatic; loss of deep tendon reflexes or paresthesia

**Grade 2 (Moderate)**

- Peripheral Motor: Moderate symptoms; limiting ADLs
- Peripheral Sensory: Moderate symptoms; limiting ADLs

**Grade 3 (Severe)**

- Peripheral Motor: Severe symptoms; limiting self-care ADLs; requires assistive devices
- Peripheral Sensory: Severe symptoms; limiting self-care ADLs

**Grade 4 (Potentially Life-Threatening)**

- Peripheral Motor: Life-threatening; urgent intervention indicated
- Peripheral Sensory: Life-threatening; urgent intervention indicated

**Grade 5 (Death)**

- Early identification and evaluation of patient symptoms

**Nursing Implementation:**

- Compare baseline assessment grade 4 document neuropathy and etiology (diabetic, medication, vascular, chemotherapy)

**RED FLAGS:**

- Guillain–Barré syndrome

**Grade 1 (Mild)**

- Early identification and evaluation of patient symptoms

**Grade 2 (Moderate)**

- Peripheral Motor: Moderate symptoms; limiting ADLs
- Peripheral Sensory: Moderate symptoms; limiting ADLs

**Grade 3 (Severe)**

- Peripheral Motor: Severe symptoms; limiting self-care ADLs; requires assistive devices
- Peripheral Sensory: Severe symptoms; limiting self-care ADLs

**Grade 4 (Potentially Life-Threatening)**

- Peripheral Motor: Life-threatening; urgent intervention indicated
- Peripheral Sensory: Life-threatening; urgent intervention indicated

**Grade 5 (Death)**

- Early identification and evaluation of patient symptoms

**Nursing Implementation:**

- Compare baseline assessment grade 4 document neuropathy and etiology (diabetic, medication, vascular, chemotherapy)

**RED FLAGS:**

- Guillain–Barré syndrome

**Grade 1 (Mild)**

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- Peripheral Sensory: Life-threatening; urgent intervention indicated

**Grade 5 (Death)**

- Early identification and evaluation of patient symptoms

**Nursing Implementation:**

- Compare baseline assessment grade 4 document neuropathy and etiology (diabetic, medication, vascular, chemotherapy)

**RED FLAGS:**

- Guillain–Barré syndrome
Risk of immune-mediated nephritis is greater in patients receiving combination immunotherapy regimens and PD-1 inhibitors.

RED FLAGS:
- Educate patients and family about the rationale for discontinuation of immunotherapy in patients who develop severe nephritis.
- Educate patients that new urinary symptoms should be reported immediately.
- Monitor creatinine more frequently if levels appear to be rising, and for Grade 1 toxicity.
- Identify individuals with pre-existing renal dysfunction prior to initiating immunotherapy. Ensure baseline creatinine has been obtained.

Nursing Implementation:
- Identify barriers to adherence.
- Assess patient & family understanding of recommendations and rationale.
- Anticipate that nephrology consultation may be initiated by provider.
- Anticipate the use of IV fluid to ensure adequate hydration.
- Anticipatory guidance on proper administration.
- Upon symptoms resolution to patient's baseline, or Grade 1, creatinine or in patients with multiple comorbidities.
- Anticipate possible hospital admission for Grade 4 elevations in creatinine if creatinine does not improve within 48–72 hours.
- Anticipate that renal biopsy will be considered.
- Anticipate increased in corticosteroid dosing (i.e., treat as if in sepsis). 

Management:

**Acute Kidney Injury**

**Grading Toxicity**

- **Creatinine level >0.3 mg/dL:**
  - **Grade 1 (Mild):**
  - **Grade 2 (Moderate):**
  - **Grade 3 (Severe):**
  - **Grade 4 (Potentially Life-Threatening):**
  - **Creatinine 1.5–2×ULN:**
  - **Creatinine 2–3×ULN:**
  - **Creatinine >3×ULN or >4.0 mg/dL:**

**Definition:** A disorder characterized by the acute loss of renal function and is traditionally classified as pre-renal, renal, and post-renal.

**Care Step Pathway – Nephritis (Inflammation of the Kidneys)**

**Nursing Assessment**

**Look:**
- Does the patient look ill?
- Does the patient appear uncomfortable?

**Listen:**
- Flank pain or tenderness
- Nausea or vomiting
- Diaphoresis
- Hypertension
- Weight gain
- Edema
- Change in urine color
- Change in amount/character of urine
- Change in bowel habits

**Look:**
- Does the patient have a fever?
- Does the patient have weakness or fatigue?
In addition to acute interstitial nephritis seen from PD-1 inhibitors, there are case reports of lupus-like nephritis and granulomatous acute interstitial nephritis. The risk of immune-mediated nephritis is greater in patients receiving combination immunotherapy regimens and PD-1 inhibitors. Risk of mortality if unrecognized or treatment is delayed.

**RED FLAGS:**

- Anticipate the steroid requirements to manage immune-mediated nephritis are high (up to 1–2 mg/kg/d) and patients will be on corticosteroid therapy for at least 1 month.
- Monitor creatinine more frequently if levels appear to be rising, and for Grade 1 toxicity.
- Check kidney function prior to each dose of immunotherapy.
- Identify individuals with pre-existing renal dysfunction prior to initiating immunotherapy. Ensure baseline creatinine has been obtained.

**Nursing Implementation:**

- Identify barriers to adherence and anticipate the use of IV fluid to ensure adequate hydration.
- Anticipatory guidance on proper administration to taper corticosteroid dose slowly over 1 month.
- Anticipate increased in corticosteroid dosing (i.e., treat as if immunosuppressive medications will be considered).
- Anticipate use of additional supportive care medications.
- Hemodialysis may be considered if symptoms do not improve within 48–72 hours, and then slow taper over at least 1 month.
- Systemic corticosteroids (e.g., prednisone) 0.5–1 mg/kg/day divided every 2–3 days until improvement.
- Immunosuppressive medications to be initiated to treat immune-mediated nephritis.
- Moderate elevation in creatinine (Grade 2).
- Severe elevation in creatinine (Grade 3).
- Life-threatening consequences; dialysis indicated.

**Management:**

- Evaluate patient to maintain physical function and impact of OOL.
- Evaluate for prescriptive kidney/renal/peptide medications that may be contributing to kidney dysfunction.
- Eliminate potentially nephrotoxic medications.
- Assess for other etiologies such as infection.

**Overall Strategy**

- Anticipate continued use of immunotherapy and set subsequent visits.
- Increase frequency of concomitant radiology tests.
- Dyspnea or edema.
- Nausea.
- Symptoms concerning for:
  - Lung edema?
  - Pyelonephritis?
  - Urinary tract infection?
  - Urinalysis abnormalities (casts, hematuria, electrolyte abnormalities)
  - Presence of current or prior immune-mediated nephritis?
- Are associated symptoms present?
- How much fluid is the patient taking in? Frequency?
- Moderate elevation in creatinine (Grade 2).
- Severe elevation in creatinine (Grade 3).

**Moderate elevation in creatinine (Grade 2):**

- Early intervention to maintain physical function and impact on OOL.
- Evaluate for prescriptive kidney/renal/peptide medications that may be contributing to kidney dysfunction.
- Eliminate potentially nephrotoxic medications.
- Assess for other etiologies such as infection.
In addition to acute interstitial nephritis, patients receiving combination immunotherapy regimens and PD-1 inhibitors may develop severe nephritis. Risk of immune-mediated nephritis is greater in patients receiving combination immunotherapy regimens and PD-1 inhibitors.

- Risk of acute onset
- Risk of mortality if unrecognized or treatment is delayed

Red Flags:

- Early intervention to maintain or improve physical function and impact on QOL
- Evaluate for progressive kidney/adrenal/pelvic metastases that may be contributing to kidney dysfunction
- Eliminate potentially nephrotoxic medications
- Anticipate immunotherapy to continue
- Avoid/minimize addition of nephrotoxic herbals, vitamins, anticipating possible systemic corticosteroids (e.g., prednisone 1–2 mg/kg/day, in divided doses) until symptoms improve to baseline and then slow taper corticosteroid dose slowly over 1 month

Nursing Implications:

- Educate patients and family about the rationale for discontinuation of immunotherapy in patients who develop severe nephritis
- Anticipate the steroid requirements to manage immune-mediated nephritis are high (up to 1–2 mg/kg/d) and patients will be on concomitant therapy for at least 1 month
- Educate patients that new unexplained symptoms should be reported immediately
- Monitor creatinine prior to each dose of immunotherapy
- Check kidney function prior to each dose of immunotherapy
- Identify individuals with pre-existing renal dysfunction prior to initiating immunotherapy. Ensure baseline creatinine has been obtained
- Monitor creatinine more frequently if levels appear to be rising and for Grade 1 toxicity
- Pembrolizumab or nivolumab to be withheld for first-occurrence Grade 2 event (until Grade 0/1)
- Ipilimumab to be withheld for any Grade 2 event
- Ipilimumab to be discontinued for any Grade 3/4 event
- Corticosteroids (e.g., prednisone 1–2 mg/kg/day, in divided doses) until symptoms improve to baseline and then slow taper corticosteroid dose slowly over 1 month
- Anticipate increase in frequency of creatinine monitoring (i.e., weekly)
- Anticipate use of additional supportive care medications
- Anticipate use of IV fluid to ensure adequate hydration
- Anticipate nephrology consultation may be initiated by provider
- Anticipate possible hospital admission for Grade 4 elevations in creatinine or in patients with multiple comorbidities
- Anticipate use of additional supportive care medications
- Anticipate nephrology consultation will be initiated by provider
- Systemic corticosteroids (e.g., prednisone) to be discontinued for any Grade 3/4 event
- Pembrolizumab or nivolumab to be withheld for Grade 2 events

Concomitantly Administered Medications

- Antibiotics
- Contrast media or other nephrotoxic agents (contrast dye, aminoglycosides, PPI)?
- Antibiotics
- Urinary tract infection?
- Worsening CHF?
- Pyelonephritis?
- Are symptoms limiting ADLs?
- Malaise?
- Nausea?
- Other immune-related adverse effects?
- Is patient volume depleted?
- How much fluid is the patient taking in? Frequency? Urine color? Has there been change in urination? Does the patient appear uncomfortable?

NCI-CTCAE v4.03, American Society of Clinical Oncology (ASCO) and others

Overall Strategy

Management
### Management of other AEs associated with nivolumab monotherapy.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Common symptoms</th>
<th>Common management/anticipatory guidance</th>
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| Anorexia              | Decreased appetite                                                              | * Monitor weight; query patient about appetite/eating habits; advise dietary modification if necessary (should improve with time)  
* Anticipate standard dose holds/discontinuations*  
* Consider referral to nutrition services for counseling on best food choices to avoid excessive weight loss |
| Constipation/abdominal pain | Infrequent stools/difficulty stooling, abdominal pain                          | * Increase fluid, fiber; use laxatives with caution  
* Consider appropriate testing to evaluate bowel obstruction  
* Anticipate standard dose holds/discontinuations* for Grade 3 and Grade 4 (constipation with manual evacuation indicated, severe abdominal pain, or life-threatening consequences) |
| Embryo-fetal toxicity | —                                                                               | * Advise of risk to fetus and recommend use of effective contraception during treatment and for 3 months after ipilimumab and for 5 months after nivolumab is discontinued  
* Advise patient to tell HCP immediately if they or their partner suspect they are pregnant while taking therapy |
| Encephalitis          | Headache, fever, tiredness, confusion, memory problems, sleepiness, hallucinations, seizures, stiff neck | * New-onset, moderate-to-severe symptoms: rule out infectious or other causes  
* Counsel neurologist, obtain brain MRI, and lumbar puncture  
* Anticipate standard dose-holds and discontinuations* |
| Fatigue               | Feeling tired; lack of energy                                                   | * Query patients regarding energy level; evaluate possible contributory factors, including infection, disease progression, and hematological and metabolic abnormalities; standard supportive care  
* Anticipate standard dose holds/discontinuations*  
* Fatigue that interferes with ADLs is concerning and should be evaluated for underlying causes. |
| Headache              | Head pain                                                                       | * Need to rule out brain metastases, encephalitis, or hypophysitis; otherwise, standard supportive care (should improve with time)  
* Headache occurring in conjunction with fatigue could be indicative of hypophysitis  
* Anticipate standard dose holds/discontinuations* |
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| Infusion reaction                 | Chills/shaking, back pain, itching, flushing, difficulty breathing, hypotension, fever | * Nivolumab and/or ipilimumab: For mild/moderate (Grade 1–2) reactions: interrupt or slow rate of infusion; monitor to recovery.  
* For severe/life-threatening (Grade 3–4) reactions: Discontinue nivolumab and/or ipilimumab; manage anaphylaxis via institutional protocol; monitor. Premedication with an antipyretic and antihistamine may be considered for future doses |
| Insomnia                          | Difficulty falling or staying asleep                                            | * Counsel patients on good sleep habits; prescription medications can be used if needed (Should improve over time)  
* Anticipate standard dose holds/discontinuations*                                                                                                                                                                                    |
| Nausea/vomiting                   | Vomiting, queasiness, RUQ or LUQ pain                                           | * Standard supportive care is usually adequate  
* May indicate hepatotoxicity; check LFTs/lipase/amylase  
* Anticipate standard dose holds/discontinuations*                                                                                                                                                                                   |
| Upper respiratory tract infection | Cough, runny nose, sore throat, nasal breathing                                  | * Evaluate potential causes—a dry cough and shortness of breath would increase concern for pneumonitis  
* Standard supportive care  
* Anticipate standard treatment holds*                                                                                                                                                                                           |

*Withhold nivolumab for any Grade 3 (severe) AE. Permanently discontinue for any Grade 4 (life-threatening) AE, persistent Grade 2–3 AE, any severe (Grade 3) AE that recurs, or when ≥10 mg/d prednisone or equivalent is required for 12 weeks. Resume treatment when AE returns to Grade 0 or 1.