Pembrolizumab (Keytruda®) 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 inhibitory role 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. Pembrolizumab selectively binds to PD-1, thus blocking the inhibitory pathway and releasing the immune system. This allows the immune response to occur.

Pembrolizumab is indicated as monotherapy for the treatment of unresectable or metastatic (advanced) melanoma and for various other cancer types.

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.
For advanced melanoma, the recommended dose of pembrolizumab (Keytruda®) is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.

Pembrolizumab solution is clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed.

Pembrolizumab is provided as 50 mg lyophilized powder in a single-dose vial for reconstitution or as a 100 mg/4 mL (24 mg/mL) solution in a single-dose vial. When reconstituting pembrolizumab for injection, slowly swirl the vial. Do NOT shake the vial.

Pembrolizumab is classified as an irritant and may be safely administered via a central or peripheral line. It is important to assure IV access before administration. Pembrolizumab should be administered through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding in-line or add-on filter (pore size of 0.2 – 5 micrometers).
SIDE EFFECTS AND THEIR MANAGEMENT

Because pembrolizumab is an immunotherapy that works by enhancing the patient’s immune system, most adverse reactions associated with pembrolizumab are related to overactivity of the patient’s immune system (i.e., 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 may be necessary (mycophenolate mofetil, cyclophosphamide, etc)
  » Pembrolizumab will likely be held or discontinued depending on severity and/or persistence
  » Referral to organ specialist should be considered, given that unique testing and management strategies may be required

• irAEs associated with pembrolizumab treatment can be categorized into those that are most common, less common but serious, and others that are easily overlooked. (Table 1; Appendix 1). Other adverse events associated with pembrolizumab therapy are listed in Appendix 2.

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

<table>
<thead>
<tr>
<th>irAE category</th>
<th>Examples</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most common</td>
<td>Skin toxicities (pruritis, rash, etc) Gastrointestinal toxicities</td>
<td>Appendix 1</td>
</tr>
<tr>
<td></td>
<td>- Mild diarrhea/colitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Mucositis/xerostomia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hepatic toxicities</td>
<td></td>
</tr>
<tr>
<td>Less common but serious</td>
<td>Endocrinopathies</td>
<td>Appendix 1</td>
</tr>
<tr>
<td></td>
<td>- Hypophysitis (pituitary)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Thyroiditis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Diabetes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pneumonitis</td>
<td></td>
</tr>
<tr>
<td>Easily overlooked</td>
<td>Arthralgia/arthritis</td>
<td>Appendix 1</td>
</tr>
<tr>
<td></td>
<td>Neuropathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nephritis</td>
<td></td>
</tr>
</tbody>
</table>
CLINICAL PEARLS

• PD-L1 status or elevated expression in not a prerequisite for pembrolizumab treatment of advanced melanoma, as it is in lung cancer

• Pembrolizumab-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 occurrence of irAEs during the tapering period

• Endocrinopathies tend to occur somewhat more commonly with pembrolizumab 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 pembrolizumab regimen with them at all times. This might be the pembrolizumab-specific wallet card, or at least emergency phone numbers and the 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
QUESTIONS & ANSWERS

Q. How long will patients stay on pembrolizumab?

A. The prescribing information indicates until disease progression or unacceptable toxicity. The interpretation of these criteria varies from institution to institution and from provider to provider.

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

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

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

A. Generally, the safety profile of pembrolizumab 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) 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.
PATIENT RESOURCES

Financial Assistance
The Merck Access Program
1-855-257-3932
www.keytruda.com/keytruda-cost/

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

American Cancer Society Resource Section


# Care Step Pathway - Skin Toxicities

## Nursing Assessment

### Look:
- Does the patient appear uncomfortable?
- Does the patient appear unwell?
- Is there an obvious rash?
- Is the patient scratching during the visit?
- Is skin integrity intact?
- Are there skin changes?
  - Xerosis
  - Changes in skin pigment or color
- Is there oral involvement of the rash?

### Listen:
- Does the patient have pruritus with or without rash?
- Are symptoms interfering with ADLs?
- Have symptoms worsened?

### Recognize:
- Is there a history of dermatitis, pre-existing skin issues (psoriasis, wounds, etc.)?
- Laboratory abnormalities consistent with other etiologies (e.g., eosinophils on complete blood count, liver function abnormalities)

## Grading Toxicity

### MACULOPAPULAR RASH (aka morbilliform rash)
**Definition:** A disorder characterized by the presence of macules (flat) and papules (elevated); frequently affecting the upper trunk, spreading centripetally and associated with pruritus

<table>
<thead>
<tr>
<th>Grade 1 (Mild)</th>
<th>Grade 2 (Moderate)</th>
<th>Grade 3 (Severe)</th>
<th>Grade 4 (Potentially Life-Threatening)</th>
<th>Grade 5 (Death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macules/papules covering &lt;10% BSA with or without symptoms (e.g., pruritus, burning, tightness)</td>
<td>Macules/papules covering 10-30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADLs</td>
<td>Macules/papules covering &gt;30% BSA with or without associated symptoms; limiting self-care ADLs; skin sloughing covering &lt;10% BSA</td>
<td>Papules/pustules covering any % BSA with or without symptoms and associated with superinfection requiring IV antibiotics; skin sloughing covering 10-30% BSA</td>
<td></td>
</tr>
</tbody>
</table>

### PRURITUS
**Definition:** A disorder characterized by an intense itching sensation

<table>
<thead>
<tr>
<th>Grade 1 (Mild)</th>
<th>Grade 2 (Moderate)</th>
<th>Grade 3 (Severe)</th>
<th>Grade 4 (Potentially Life-Threatening)</th>
<th>Grade 5 (Death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild or localized; topical intervention indicated</td>
<td>Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); limiting instrumental ADLs</td>
<td>Intense or widespread; constant; limiting self-care ADL or sleep</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Management

**Overall Strategy**
- Assess for other etiology of rash: ask patient about new medications, herbals, supplements, alternative/complementary therapies, lotions, etc.

### Interventions in at-risk patients
- Advise gentle skin care:
  - Avoid soap. Instead, use non-soap cleansers that are fragrance- and dye-free (use mild soap on the axillae, genitalia, and feet)
  - Daily applications of non-steroidal moisturizers or emollients containing humectants (urea, glycerin)
  - Apply moisturizers and emollients in the direction of hair growth to minimize development of folliculitis
- Advise sun-protective measures
- Assess patient & family understanding of prevention strategies and rationale
- Identify barriers to adherence

### Grade 1 (Mild)
- Immunotherapy to continue
- Oral antihistamines will be used in some patients
- Topical corticosteroids will be used in some patients (0.5 mg/kg)
- Advise vigilant skin care
  - Increase to twice daily applications of non-steroidal moisturizers or emollients applied to moist skin
  - Moisturizers with ceramides and lipids are advised; however, if cost is an issue, petroleum jelly is also effective
- Soothing methods
  - Cool cloth applications
  - Topicals with cooling agents such as menthol or camphor
  - Refrigerating products prior to application
  - Avoid hot water; bathe or shower with tepid water
  - Keep fingernails short
  - Cool temperature for sleep
- Advise strict sun protection
- Monitor vigilantly. Instruct patient & family to call clinic with any sign of worsening rash/symptoms. Anticipate office visit for evaluation
- Assess patient & family understanding of skin care recommendations and rationale
- Identify barriers to adherence

### Grade 2 (Moderate)
- Ipilimumab will be withheld for any Grade 2 event
- Oral corticosteroids (0.5 mg/kg–1.0 mg/kg) and oral antihistamines/oral anti-pruritics to be used
- Consider dermatology consult
- Patient education:
  - Proper administration of oral corticosteroids
    - Take with food
    - Take early in day
  - Concomitant medications may be prescribed
    - H2 blocker
    - Antibiotic prophylaxis
- Advise vigilant skin care
  - Gentle skin care
  - Tepid baths; oatmeal baths
- Advise strict sun protection
- Assess patient & family understanding of toxicity and rationale for treatment hold
- Identify barriers to adherence

### Grades 3-4 (Severe or Life-Threatening)
- Nivolumab to be withheld for Grade 3 rash or confirmed SJS or TEN
- Ipilimumab to be discontinued for any Grade 3/4 event, and nivolumab for Grade 4 rash or confirmed SJS or TEN
- Pembrolizumab or nivolumab to be discontinued for any Grade 3/4 event that recurs, persists ≥12 weeks, or for inability to reduce steroid dose to ≤10 mg prednisone or equivalent within 12 weeks
- Anticipate hospitalization and initiation of IV corticosteroids (1.5–2.0 mg/kg)
- Anticipate dermatology consult +/- biopsy
- Provide anticipatory guidance:
  - Rationale for hospitalization and treatment discontinuation
  - Rationale for prolonged steroid taper
  - Side effects of high-dose steroids
  - Risk of opportunistic infection and need for antibiotic prophylaxis
  - Effects on blood sugars, muscle atrophy, etc.
- Assess patient & family understanding of toxicity and rationale for treatment discontinuation
- Identify barriers to adherence, specifically compliance with steroids when transitioned to oral corticosteroids

**RED FLAGS:**
- Extensive rash (>50% BSA), or rapidly progressive
- Oral involvement
- Concern for suprainfection

ADLs = activities of daily living; BSA = body surface area; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis
Care Step Pathway - Gastrointestinal Toxicity: Diarrhea and Colitis

<table>
<thead>
<tr>
<th>Look:</th>
<th>Nursing Assessment</th>
<th>Recognize:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Does the patient appear weak?</td>
<td>Listen:</td>
<td>- Serum chemistry/hematology abnormalities</td>
</tr>
<tr>
<td>- Has the patient lost weight?</td>
<td>- Quantity &amp; quality of bowel movements (e.g., change in/</td>
<td>- Infectious vs immune-related adverse event causation</td>
</tr>
<tr>
<td>- Does the patient appear dehydrated?</td>
<td>increased frequency over baseline): solid, soft, or liquid</td>
<td>- Peritoneal signs of bowel perforation (i.e., pain, tenderness, bloating)</td>
</tr>
<tr>
<td>- Does the patient appear in distress?</td>
<td>diarrhea; dark or bloody stools; or stools that float</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Fever</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Abdominal pain or cramping</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Increased fatigue</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Upset stomach, nausea, or vomiting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Bloating/increased gas</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Decreased appetite or food aversions</td>
<td></td>
</tr>
</tbody>
</table>

**Grading Toxicity**

**Diarrhea (increased frequency, loose, large volume, or liquidy stools)**

- **Grade 1 (Mild)**
  - Increase of <4 stools/day over baseline
  - Mild increase in ostomy output compared with baseline

- **Grade 2 (Moderate)**
  - Increase of 4–6 stools/day over baseline
  - Moderate increase of output in ostomy compared with baseline

- **Grade 3 (Severe)**
  - Increase of ≥7 stools/day over baseline; incontinence
  - Hospitalization indicated
  - Severe increase in ostomy output compared with baseline
  - Limiting self-care ADLs

- **Grade 4 (Potentially Life-Threatening)**
  - Life-threatening (e.g., perforation, bleeding, ischemic necrosis, toxic megacolon)
  - Urgent intervention required

- **Grade 5 (Death)**

**Colitis (inflammation of the intestinal lining)**

- **Grade 1 (Mild)**
  - Asymptomatic; clinical or diagnostic observation only; intervention not indicated

- **Grade 2 (Moderate)**
  - Abdominal pain; blood or mucus in stool

- **Grade 3 (Severe)**
  - Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs

- **Grade 4 (Potentially Life-Threatening)**
  - Life-threatening (e.g., hemodynamic collapse); urgent intervention indicated

- **Grade 5 (Death)**
### Management (including Anticipatory Guidance)

**Overall Strategy:**
- Rule out infectious, non-infectious, disease-related etiologies

### Grade 1 (Mild)
- May continue immunotherapy

**Diet modifications (very important):**
- Institute bland diet; decrease fiber, uncooked fruits/vegetables, red meats, fats, dairy, oil, caffeine, alcohol, sugar

### Grade 2 (Moderate)
- Send stool sample for *C difficile* testing, culture, and ova and parasite
- Immunotherapy to be withheld until Grade ≤1 or patient’s baseline (ipilimumab, pembrolizumab, nivolumab)
- Provide anti-diarrheals: Imodium® (loperamide) or Lomotil® (diphenoxylate/atropine)
- If upper or lower GI symptoms persist >5–7 days
  - Oral steroids* to be started (prednisone 0.5 mg–1 mg/kg/day or equivalent)
  - After control of symptoms, a ≥4-week steroid* taper will be initiated
- Immunotherapy to be discontinued if Grade 2 symptoms persist ≥6 weeks (ipilimumab) or ≥12 weeks (pembrolizumab, nivolumab), or for inability to reduce steroid dose to ≤7.5 mg (ipilimumab) or ≤10 mg prednisone or equivalent (pembrolizumab, nivolumab) within 12 weeks

**Diet modification:**
- Institute bland diet low in fiber, residue, and fat (BRAT [Bananas, Rice, Applesauce, Toast] diet)
- Decrease fiber, uncooked fruit and vegetables, red meats, fats, dairy, oil, caffeine, alcohol, sugar
- Avoid laxatives or stool softeners
- Advance diet slowly as steroids are tapered,* reduced to low doses and assess for loose or liquid stool for several days or longer
- Steroids* to be tapered slowly over at least 4 weeks

**(Moderate) persistent or relapsed symptoms with steroid* taper**
- Consider gastroenterology consult for possible intervention (flex sig/colonoscopy/endoscopy)
- IV steroids* to be started at 1 mg/kg/day
- Immunotherapy to be held until ≤Grade 1
- Control symptoms, then ≥4-week steroid* taper
- Recurrent diarrhea is more likely when treatment is restarted

### Grades 3-4 (Severe or Life-Threatening)
- Onset:
  - Continued diet modification, anti-diarrheals, and steroid titration
- Immunotherapy:
  - Grade 3: Pembrolizumab or nivolumab to be withheld when used as single agent; ipilimumab to be discontinued as single agent and nivolumab when given with ipilimumab
  - Grade 4: Ipilimumab and/or PD-1 inhibitor to be discontinued
- Does of steroids* to be increased:
  - Steroids* 1-2 mg/kg/day prednisone or equivalent: methylprednisolone (Solu-Medrol®) 1 g IV (daily divided) doses
  - Steroid taper instructions/calendar as a guide but not an absolute
  - Hospitalization
  - GI consultation
  - Assess for peritoneal signs, perforation (NPO & abdominal x-ray, surgical consult prn)
  - Use caution with analgesics (opioids) and anti-diarrheals
  - Consider gastroenterology consult for possible intervention
  - Infliximab infusion delay may have life-threatening consequences
  - PPD (tuberculin) testing not required in this setting

**Steroids* refractory:** (if not responsive within 72 hours to high-dose IV steroid* infusion)
- Infliximab (Remicade®) 5 mg/kg infusion may be considered
- Infliximab infusion delay may have life-threatening consequences

**Diet modification:**
- Very strict with acute symptoms: clear liquids; very bland, low fiber and low residue (BRAT diet)
- Advance diet slowly as steroids* reduced to low doses
- Steroids* to be tapered slowly over at least 4 weeks

**Supportive medications for symptomatic management:**
- Loperamide: 2 capsules at the onset & 1 with each diarrhea stool thereafter, with a maximum of 6 per day
- Diphenoxylate/atropine 1-4 tablets per day
- Simethicone when necessary
**Nursing Implementation:**
- Compare baseline assessment: grade & document bowel frequency
- Early identification and evaluation of patient symptoms
- Grade symptom & determine level of care and interventions required
- Early intervention with lab work and office visit if colitis symptoms are suspected

*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 & 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

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

ADLs = activities of daily living; PD-1 = programmed cell death protein 1
## Care Step Pathway - Mucositis & Xerostomia

### Nursing Assessment

**Look:**
- Does the patient appear uncomfortable?
- Does the patient appear unwell?
- Difficulty talking?
- Licking lips to moisten often?
- Weight loss?
- Does the patient appear dehydrated?
- Does the patient have thrush?

**Listen:**
- Does the patient report?
  - Mouth pain (tongue, gums, buccal mucosa)
  - Mouth sores
  - Difficulty eating
  - Waking during the sleep to sip water
  - Recent dental-related issues
  - Need for dental work (e.g., root canal, tooth extraction)
- Have symptoms worsened?

**Recognize:**
- A history of mouth sores
- Does patient smoke?
- Concomitant medications associated with causing dry mouth?
- Reports of dry mouth often accompany mucositis
- Other reports of dry membranes (e.g., eyes, nasal passages, vagina)

### Grading Toxicity

#### Oral Mucositis
Definition: A disorder characterized by inflammation of the oral mucosa

<table>
<thead>
<tr>
<th>Grade 1 (Mild)</th>
<th>Grade 2 (Moderate)</th>
<th>Grade 3 (Severe)</th>
<th>Grade 4 (Potentially Life-Threatening)</th>
<th>Grade 5 (Death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic or mild symptoms; intervention not indicated</td>
<td>Moderate pain; not interfering with oral intake; modified diet indicated</td>
<td>Severe pain; interfering with oral intake</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Life-threatening</td>
</tr>
</tbody>
</table>

#### Xerostomia (dry mouth)
Definition: A disorder characterized by reduced salivary flow in the oral region

<table>
<thead>
<tr>
<th>Grade 1 (Mild)</th>
<th>Grade 2 (Moderate)</th>
<th>Grade 3 (Severe)</th>
<th>Grade 4 (Potentially Life-Threatening)</th>
<th>Grade 5 (Death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic (e.g., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow &gt;0.2 mL/min</td>
<td>Moderate symptoms; oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 mL/min</td>
<td>Inability to adequately aliment orally; tube feeding or total parenteral nutrition indicated; unstimulated saliva &lt;0.1 mL/min</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Life-threatening</td>
</tr>
</tbody>
</table>
### Management (Including anticipatory guidance)

#### Overall Strategy
- Assess for other etiologies of mucositis or dry mouth: candidiasis; ask patient about new medications (particularly antihistamines), herbas, supplements, alternative/complementary therapies

<table>
<thead>
<tr>
<th>Interventions in at-risk patients</th>
<th>Grade 1 (Mild)</th>
<th>Grade 2 (Moderate)</th>
<th>Grades 3-4 (Severe or Life-Threatening)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Advise basic oral hygiene:</td>
<td>- Anticipate immunotherapy to continue</td>
<td>- Ipilimumab to be withheld for any Grade 2 event (resume when Grade 0/1)</td>
<td>- Nivolumab to be withheld for first occurrence Grade 3 event. Immunotherapy to be discontinued for any Grade 4 event or for a Grade 3 event persisting ≥12 weeks (ipilimumab, nivolumab) or any recurrent Grade 3 event (pembrolizumab, nivolumab)</td>
</tr>
<tr>
<td>o Tooth brushing (soft toothbrush, avoid toothpaste with whitening agents)</td>
<td>- Advise ongoing basic oral hygiene</td>
<td>- Immunotheapy to be discontinued for Grade 2 events persisting ≥6 (ipilimumab) or ≥12 weeks (pembrolizumab, nivolumab)</td>
<td>- Anticipate hospitalization if unable to tolerate oral solids or liquids</td>
</tr>
<tr>
<td>o Use of dental floss daily</td>
<td>- Advise avoidance of hot, spicy, acidic foods</td>
<td>- Assess for Sicca syndrome, Sjögren’s syndrome</td>
<td>- Unclear role of systemic corticosteroids</td>
</tr>
<tr>
<td>o ≥1 mouth rinses to maintain oral hygiene (avoid commercial mouthwashes or those with alcohol)</td>
<td>- Anticipate possible alternative treatment(s)</td>
<td>- Encourage vigilant oral hygiene</td>
<td>- Anticipate need for supplemental nutrition</td>
</tr>
</tbody>
</table>
| - If patient wears dentures, assess for proper fit, areas of irritation, etc. | - Zinc supplements or 0.2% zinc sulfate mouthwash | - Xerostomia: | - Analgesics
|  - Dental referral if necessary | o Probiotics with Lactobacillus | - Advise moistening agents | o Analgesics
|  - Assess patient & family understanding of prevention strategies and rationale | - Benzydamine HCl | o Saliva substitute | - Systemic opioids may be indicated |
|  o Identify barriers to adherence | - Assess patient & family understanding of recommendations and rationale | o Synthetic saliva | - Oral care |
| - Monitor hydration status | - Identify barriers to adherence | o Oral lubricants | - Assess patient & family understanding of toxicity and rationale for interventions as well as treatment discontinue |
| - Monitor weight | - Advise secretagogues | o Nonpharmacologic | o Identify barriers to adherence |
|  - Dexamethasone oral solution | o Saliva substitute |  o Sugarless gum | |  o Synthentic saliva |
|  - Corticosteroid rinses | o Synthetic saliva |  o Sugarless hard candies | |  o Pilocarpine |
|  - “Miracle Mouthwash”: | o Oral lubricants |  o Natural lemon | |  o Cevimeline HCl |
|  - 0.5% doxepin mouthwash | o Nonpharmacologic |  o Pharmacologic | |  |
|  - 2% viscous lidocaine applied to lesions 15 minutes prior to meals | o Pilocarpine |  o Corticosteroid rinses | |  |
|  - Gelclair®, Zilactin® | o Cevimeline HCl |  - Dexamethasone oral solution | |  |
|  - 2% viscous lidocaine applied to lesions 15 minutes prior to meals | o Synthetic saliva |  - Monitor weight | |  o Monitor hydration status |
|  - Miracle Mouthwash”: diphenhydramine/lidocaine/simethicone | o Oral lubricants |  - Nutrition referral if appropriate | |  |

### Overall Strategy
- Assess for other etiologies of mucositis or dry mouth: candidiasis; ask patient about new medications (particularly antihistamines), herbas, supplements, alternate/complementary therapies

### Interventions in at-risk patients
- Advise basic oral hygiene:
  - Tooth brushing (soft toothbrush, avoid toothpaste with whitening agents)
  - Use of dental floss daily
  - ≥1 mouth rinses to maintain oral hygiene (avoid commercial mouthwashes or those with alcohol)
- If patient wears dentures, assess for proper fit, areas of irritation, etc.
- Dental referral if necessary
- Assess patient & family understanding of prevention strategies and rationale
- Identify barriers to adherence

### Grade 1 (Mild)
- Anticipate immunotherapy to continue
- Advise ongoing basic oral hygiene
- Advise avoidance of hot, spicy, acidic foods
- Anticipate possible alternative treatment(s)
- Zinc supplements or 0.2% zinc sulfate mouthwash
- Probiotics with Lactobacillus
- Benzydamine HCl
- Assess patient & family understanding of recommendations and rationale
- Identify barriers to adherence

### Grade 2 (Moderate)
- Ipilimumab to be withheld for any Grade 2 event (resume when Grade 0/1)
- Immunotherapy to be discontinued for any Grade 2 event persisting ≥6 (ipilimumab) or ≥12 weeks (pembrolizumab, nivolumab)
- Assess for Sicca syndrome, Sjögren’s syndrome
- Encourage vigilant oral hygiene

### Xerostomia:
- Advise moistening agents
  - Saliva substitute
  - Synthetic saliva
  - Oral lubricants
- Advise secretagogues
  - Nonpharmacologic
    - Sugarless gum
    - Sugarless hard candies
    - Natural lemon
  - Pharmacologic
    - Pilocarpine
    - Cevimeline HCl

### Mucositis:
- Vigilant oral hygiene
  - Increase frequency of brushing to Q4 hours and at bedtime
  - If unable to tolerate brushing, advise chlorhexidine gluconate 0.12% or sodium bicarbonate rinses
    - 1 tsp baking soda in 8 ounces of water or
    - ½ tsp salt and 2 tbsp sodium bicarbonate dissolved in 4 cups of water
- Encourage sips of cool water or crushed ice
  - Encourage soft, bland non-acidic foods
  - Anticipatory guidance regarding use of pharmacologic agents (as applicable)
    - Analgesics
      - Gelclair®, Zilactin®
      - 2% viscous lidocaine applied to lesions 15 minutes prior to meals
      - 2% morphine mouthwash
      - 0.5% doxepin mouthwash
      - “Miracle Mouthwash”: diphenhydramine/lidocaine/simethicone
      - Corticosteroid rinses
    - Dexamethasone oral solution
  - Monitor weight
  - Monitor hydration status
  - Nutrition referral if appropriate

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Care Step Pathway – Hepatotoxicity (immunotherapy-induced inflammation of liver tissue)

**Look:**
- Does the patient appear fatigued or listless?
- Does the patient appear jaundiced?
- Does the patient appear diaphoretic?
- Does the patient have any ascites?

**Listen:**
- Change in energy level?
- Change in skin color? Yellowing?
- Change in stool color (paler)?
- Change in urine color (darker/tea colored)?
- Abdominal pain: specifically, right upper quadrant pain?
- Bruising or bleeding more easily?
- FEVERS?
- Change in mental status?
- Increased sweating?

**Recognize:**
- Elevation in LFTs
  - AST/SGOT
  - ALT/SGPT
  - Bilirubin (total/direct)
- Alteration in GI function
- Symptoms such as abdominal pain, ascites, somnolence, and jaundice
- Other potential causes (viral, drug toxicity, disease progression)

---

**Grading Toxicity: ULN**

<table>
<thead>
<tr>
<th>Grade 1 (Mild)</th>
<th>Grade 2 (Moderate)</th>
<th>Grade 3 (Severe)</th>
<th>Grade 4 (Potentially Life-Threatening)</th>
<th>Grade 5 (Death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST/ALT:</td>
<td>AST/ALT:</td>
<td>AST/ALT:</td>
<td>AST/ALT:</td>
<td></td>
</tr>
<tr>
<td>&gt;ULN – 3.0× ULN</td>
<td>&gt;3.0× – 5.0× ULN</td>
<td>&gt;5.0× – 20.0× ULN</td>
<td>&gt;20× ULN</td>
<td></td>
</tr>
<tr>
<td>Bilirubin:</td>
<td>Bilirubin:</td>
<td>Bilirubin:</td>
<td>Bilirubin:</td>
<td></td>
</tr>
<tr>
<td>&gt;ULN – 1.5× ULN</td>
<td>&gt;1.5× – 3.0× ULN</td>
<td>&gt;3.0× ULN</td>
<td>&gt;10× ULN</td>
<td></td>
</tr>
</tbody>
</table>

**Care Step Pathway**

*Elevations in LFTs exceeding upper limits of normal (ULN) may be indicative of hepatotoxicity.*

**Hepatotoxicity**

- AST/SGOT
- ALT/SGPT
- Bilirubin (total/direct)

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

**RED FLAGS:**

- Avoid alcohol/acetaminophen or other hepatotoxins
- 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:**

- Be alert to recurring symptoms as steroids taper down & report them (taper may need to be adjusted)
- Review steroid medications side effects: mood changes (anger, reactive, hyperaware, euphoric, mania), increased appetite, interrupted sleep, oral thrush, fluid retention
- Anti-acid therapy daily as gastric ulcer prevention while on steroids

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

**Grade LFTs and any other accompanying symptoms 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:**

- 4 weeks steroids* to be tapered
- If LFT normalized and symptoms resolved, weekly days: decrease LFT checks to q3 days, then
- If LFTs stable/declining daily for 5 consecutive
- 0-1, consider resuming treatment
- Consider liver biopsy
- Once patient returns to baseline or Grade 4 slowly over ≥ 4 weeks when function recovers
- Antithymocyte globulin infusion
- 0-1000 mg po q 12 hours OR
- CellCept® (mycophenolate mofetil) 500 mg
- Consider hospital admission for IV steroids* potential for ADDING to regimen: or for inability to reduce steroid dose to
- Admission for IV steroids* potential for ADDING to steroid regimen:
- or for inability to reduce steroid dose to
- Immunotherapy may be withheld; recheck
- Consider starting steroids* 0.5 mg – 1 – 7.5 mg prednisone or equivalent per day
- Daily LFTs
- R/O hepatitis infection (acute infection or disease progression)

---

*For any recurrent Grade 3 event, and nivolumab or ipilimumab to be discontinued.

**Immunotherapy to be withheld for first-occurrence**

**Immunotherapy to be discontinued**

**Daily LFTs**

**Steroids* to be initiated at 2 mg/kg/day**

**Hospital admission**

**Steroids* to be initiated at 2 mg/kg/day**

**Immunotherapy to be withheld; recheck**

**Steroids* to be initiated at 2 mg/kg/day**

**Immunotherapy to be discontinued**

**Steroids* to be initiated at 2 mg/kg/day**

**Immunotherapy to be withheld for first-occurrence**

**Immunotherapy to be discontinued**
Management (including anticipatory guidance)

**Overall Strategy:**
- LFTs should be checked and results reviewed prior to each dose of immunotherapy
- Rule out infectious, non-infectious, and malignant causes. Consider assessing for new onset or re-activation of viral hepatitis, medications (acetaminophen, statins, and other hepatotoxic meds, or supplements/herbals), recreational substances (alcohol); consider disease progression

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

<table>
<thead>
<tr>
<th>Grade 1 (Mild)</th>
<th>Grade 2 (Moderate)</th>
<th>Grade 3 (Severe)</th>
<th>Grade 4 (Life-Threatening)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Immunotherapy may be withheld if LFTs are trending upward; recheck LFTs within ~ 1 week</td>
<td>- Immunotherapy to be withheld; recheck LFTs daily x 3 days or every 3 days; to be resumed when complete/partial resolution of adverse reaction (Grade 0/1)</td>
<td>- Steroids* to be initiated at 2 mg/kg/day prednisone or equivalent daily oral</td>
<td>- Immunotherapy to be discontinued</td>
</tr>
<tr>
<td></td>
<td>- Immunotherapy to be discontinued for Grade 2 events lasting ≥6 (ipilimumab) or ≥12 weeks (pembrolizumab, nivolumab), or for inability to reduce steroid dose to 7.5 mg prednisone or equivalent per day</td>
<td>- Nivolumab to be withheld for first-occurrence Grade 3 event. Ipilimumab to be discontinued for any Grade 3 event, and nivolumab or pembrolizumab for any recurrent Grade 3 event or Grade 3 event persisting ≥12 weeks</td>
<td>- Hospital admission</td>
</tr>
<tr>
<td></td>
<td>- Considering starting steroids* 0.5 mg – 1 mg/kg/day prednisone or equivalent daily (IV methylprednisolone 125 mg total daily dose) + an anti-acid</td>
<td>- Admission for IV steroids*</td>
<td>- Steroids* to be initiated at 2 mg/kg/day prednisone or equivalent daily intravenous</td>
</tr>
<tr>
<td></td>
<td>- Consider starting hospital admission for IV steroids*</td>
<td>- R/O hepatitis infection (acute infection or reactivation)</td>
<td>- R/O hepatitis infection</td>
</tr>
<tr>
<td></td>
<td>- If LFT normalized and symptoms resolved, steroids* to be tapered over ≥ 4 weeks when function recovers</td>
<td>- Daily LFTs</td>
<td>- Daily LFTs</td>
</tr>
<tr>
<td></td>
<td>- Once patient returns to baseline or Grade 0-1, consider resuming treatment</td>
<td>- If sustained elevation is significant and/or refractory to steroids* potential for ADDING to steroid regimen:</td>
<td>- If sustained elevation and refractory to steroids* potential for ADDING to steroid regimen:</td>
</tr>
</tbody>
</table>

**Hepatotoxicity:**

- Infliximab infusions are not recommended due to potential hepatotoxic effects.
- Overall Strategy:
  - LFTs should be checked and results reviewed prior to each dose of immunotherapy.
  - Rule out infectious, non-infectious, and malignant causes. Consider assessing for new onset or re-activation of viral hepatitis, medications (acetaminophen, statins, and other hepatotoxic meds, or supplements/herbals), recreational substances (alcohol); consider disease progression.

**Management (including anticipatory guidance):**

- **Grade 1 (Mild):** Immunotherapy may be withheld if LFTs are trending upward; recheck LFTs within ~ 1 week.
- **Grade 2 (Moderate):** Immunotherapy to be withheld; recheck LFTs daily x 3 days or every 3 days; to be resumed when complete/partial resolution of adverse reaction (Grade 0/1).
- **Grade 3 (Severe):** Steroids* to be initiated at 2 mg/kg/day prednisone or equivalent daily oral.
- **Grade 4 (Life-Threatening):** Immunotherapy to be discontinued.

**Overall Strategy:**

- LFTs should be checked and results reviewed prior to each dose of immunotherapy.
- Rule out infectious, non-infectious, and malignant causes. Consider assessing for new onset or re-activation of viral hepatitis, medications (acetaminophen, statins, and other hepatotoxic meds, or supplements/herbals), recreational substances (alcohol); consider disease progression.

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

**Management (including anticipatory guidance):**

- **Grade 1 (Mild):** Immunotherapy may be withheld if LFTs are trending upward; recheck LFTs within ~ 1 week.
- **Grade 2 (Moderate):** Immunotherapy to be withheld; recheck LFTs daily x 3 days or every 3 days; to be resumed when complete/partial resolution of adverse reaction (Grade 0/1).
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**Overall Strategy:**

- LFTs should be checked and results reviewed prior to each dose of immunotherapy.
- Rule out infectious, non-infectious, and malignant causes. Consider assessing for new onset or re-activation of viral hepatitis, medications (acetaminophen, statins, and other hepatotoxic meds, or supplements/herbals), recreational substances (alcohol); consider disease progression.

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

**Management (including anticipatory guidance):**

- **Grade 1 (Mild):** Immunotherapy may be withheld if LFTs are trending upward; recheck LFTs within ~ 1 week.
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**Overall Strategy:**

- LFTs should be checked and results reviewed prior to each dose of immunotherapy.
- Rule out infectious, non-infectious, and malignant causes. Consider assessing for new onset or re-activation of viral hepatitis, medications (acetaminophen, statins, and other hepatotoxic meds, or supplements/herbals), recreational substances (alcohol); consider disease progression.

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

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- **Grade 2 (Moderate):** Immunotherapy to be withheld; recheck LFTs daily x 3 days or every 3 days; to be resumed when complete/partial resolution of adverse reaction (Grade 0/1).
- **Grade 3 (Severe):** Steroids* to be initiated at 2 mg/kg/day prednisone or equivalent daily oral.
- **Grade 4 (Life-Threatening):** Immunotherapy to be discontinued.
**Nursing Implementation:**
- Review LFT results prior to administration of immunotherapy
- Early identification and evaluation of patient symptoms
- Early intervention with lab work and office visit if hepatotoxicity is suspected
- Grade LFTs and any other accompanying symptoms

*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 & 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

**RED FLAGS:**
- Severe abdominal pain, ascites, somnolence, jaundice, mental status changes

ALT = alanine aminotransferase; AST = aspartate aminotransferase; GI = gastrointestinal; LFT = liver function test; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; ULN = upper limit of normal
## Nursing Assessment

**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 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

## Grading Toxicity (Overall)

<table>
<thead>
<tr>
<th>Grade 1 (Mild)</th>
<th>Grade 2 (Moderate)</th>
<th>Grade 3 (Severe)</th>
<th>Grade 4 (Potentially Life-Threatening)</th>
<th>Grade 5 (Death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic or mild symptoms; clinical or diagnostic observation only (headache, fatigue)</td>
<td>Moderate symptoms; limiting age-appropriate instrumental ADLs (headache, fatigue)</td>
<td>Severe or medically significant symptoms; limiting self-care ADL (sepsis, severe ataxia)</td>
<td>Urgent intervention required (sepsis, severe ataxia)</td>
<td></td>
</tr>
</tbody>
</table>

## 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
- 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)

**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 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

**Acting on RED FLAGS:**
- Symptoms of adrenal insufficiency

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.
Care Step Pathway – Thyroiditis (inflammation of the thyroid gland)

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?

Type of Thyroid Abnormality

<table>
<thead>
<tr>
<th>TSH low or &lt;0.01 mIU/L with normal or high free T3 or T4</th>
<th>TSH &gt;5, &lt;10 mIU/L with normal free T4, T3</th>
<th>TSH &gt;10 mIU/L with normal or low free T4 &amp; T3</th>
<th>TSH low or &lt;0.01 mIU/L with high free T4 or T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Acute thyroiditis</td>
<td>Subclinical hypothyroidism</td>
<td>Primary hypothyroidism</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>- Rarely Graves’-like disease</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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Management

TSH low or <0.01 mIU/L with normal free T3 or T4
- 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 hold for symptomatic patients (e.g., beta blockers for tachycardia/murmur and immunotherapy holds for patients who have acute thyroiditis threatening an airway). Therapy is often restarted when symptoms are mild/tolerable

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

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)

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
### 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?

**Listen:**
- Frequent urination?
- Increased thirst?
- Increased hunger?
- Increased fatigue?
- Altered level of consciousness with advanced cases

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

### Grading Toxicity (Based on Fasting Glucose)

<table>
<thead>
<tr>
<th>Grade 1 (Mild)</th>
<th>Grade 2 (Moderate)</th>
<th>Grade 3 (Severe)</th>
<th>Grade 4 (Potentially Life-Threatening)</th>
<th>Grade 5 (Death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose value &gt;ULN – 160 mg/dL</td>
<td>Fasting glucose value &gt;160 – 250 mg/dL</td>
<td>Fasting glucose value &gt;250 – 500 mg/dL, hospitalization indicated</td>
<td>Fasting glucose value &gt;500 mg/dL, life-threatening consequences</td>
<td></td>
</tr>
</tbody>
</table>

### Management

**Overall Strategy:**
- Immunotherapy may be withheld until blood glucose is regulated
- Insulin therapy
- Hydration
- Endocrine consult

**Nursing Implementation:**
- Discuss that DM1 will likely be permanent
- Review signs and symptoms of hyper/hypoglycemia
- Follow patients closely with checks on blood glucose levels, fruity breath, and other symptoms (e.g., increased infections)
- Assure early intervention
- Provide insulin education (or refer)
- Discuss possibility of other immune-related AEs, including others of endocrine origin

DM = diabetes mellitus; ULN = upper limit of normal
Care Step Pathway – Pneumonitis (inflammation of lung alveoli)

### Nursing Assessment

**Look:**
- Does the patient appear uncomfortable?
- Did the patient have difficulty walking to the exam room? Or going up stairs?
- Does the patient appear short of breath?
- Is the patient tachypneic?
- Does the patient appear to be in respiratory distress?

**Listen:**
- Has the patient noted any change in breathing?
- Does the patient feel short of breath?
- Does the patient note new dyspnea on exertion?
- Does the patient notice a new cough? Or a change in an existing cough?
- Have symptoms worsened?
- Are symptoms limiting ADLs?
- Associated symptoms?
  - Fatigue
  - Wheezing

**Recognize:**
- Is the pulse oximetry low? Is it lower than baseline or compared with last visit? Is it low on exertion?
- Is there a pre-existing pulmonary autoimmune condition (i.e., sarcoidosis)?
- Is there a history of prior respiratory compromise (e.g., asthma, COPD, congestive heart failure)?
- Has the patient experienced other immune-related adverse effects?

### Grading Toxicity

#### Pneumonitis

**Definition:** A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma

<table>
<thead>
<tr>
<th>Grade 1 (Mild)</th>
<th>Grade 2 (Moderate)</th>
<th>Grade 3 (Severe)</th>
<th>Grade 4 (Potentially Life-Threatening)</th>
<th>Grade 5 (Death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic; clinical or diagnostic observations only; intervention not indicated</td>
<td>Symptomatic; medical intervention indicated; limiting instrumental ADLs</td>
<td>Severe symptoms; limiting self-care ADLs; oxygen indicated</td>
<td>Life-threatening respiratory compromise; urgent intervention indicated (tracheostomy, intubation)</td>
<td></td>
</tr>
</tbody>
</table>

#### Hypoxia

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

<table>
<thead>
<tr>
<th>Grade 1 (Mild)</th>
<th>Grade 2 (Moderate)</th>
<th>Grade 3 (Severe)</th>
<th>Grade 4 (Potentially Life-Threatening)</th>
<th>Grade 5 (Death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased oxygen saturation with exercise (e.g., pulse ox &lt;88%); intermittent supplemental oxygen</td>
<td>Decreased oxygen saturation at rest (e.g., pulse ox &lt;88%)</td>
<td></td>
<td>Life-threatening airway compromise; urgent intervention indicated (tracheostomy, intubation)</td>
<td></td>
</tr>
</tbody>
</table>
Pneumonitis

## Management

### Overall Strategy:
- Assess for other etiologies such as infection, pulmonary embolism, progressive lung metastases, or lung disease
- Early intervention to maintain or improve physical function and impact on QOL
- Assess pulse oximetry (resting & on exertion) at baseline and at each visit to assist in identifying a decrease at early onset.

<table>
<thead>
<tr>
<th>Prevention</th>
<th>Grade 1 (Mild)</th>
<th>Grade 2 (Moderate)</th>
<th>Grades 3–4 (Severe or Life-Threatening)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- No known interventions</td>
<td>- Anticipate immunotherapy to continue</td>
<td>- Immunotheapy to be withheld for Grade 2 events (resume when Grade 0/1)</td>
<td>- Discontinue immunotherapy for Grade 3/4 events</td>
</tr>
<tr>
<td></td>
<td>- Continue to monitor via radiology testing (q 2–4 weeks, as needed)</td>
<td>- Immunotherapy to be discontinued for recurrent (pembrolizumab, nivolumab) or persistent Grade 2 events (ipilimumab, pembrolizumab, nivolumab)</td>
<td>- Patient will likely need to be admitted to the hospital for further management and supportive care</td>
</tr>
<tr>
<td></td>
<td>- Review symptoms to watch for with patient and family, and remember to assess at every subsequent visit</td>
<td>- Anticipate treatment with:</td>
<td>- Anticipate the use of high-dose IV corticosteroids (e.g., methylprednisolone 2–4 mg/kg/day or equivalent)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Corticosteroids (e.g., prednisone 1–2 mg/kg/day or equivalent) until symptoms improve to baseline, and then slow taper over at least 1 month</td>
<td>- Once symptoms have resolved to baseline or Grade 1, convert to equivalent oral corticosteroid dose and then taper slowly over at least 1 month</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o If symptoms do not improve within 48–72 hours, corticosteroid dose will be escalated. IV corticosteroids may be considered</td>
<td>- Anticipate the use of empiric antibiotics until infection is excluded</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Additional supportive care medications may also be initiated</td>
<td>- Anticipate the use of additional immunosuppressive agents if symptoms do not improve in 48–72 hours (e.g., infliximab, mycophenolate, cyclophosphamide)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Anticipatory guidance on proper administration</td>
<td>- Assess patient &amp; family understanding of toxicity and rationale for treatment discontinuation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Anticipate that bronchoscopy may be ordered by provider</td>
<td>- Identify barriers to adherence, specifically compliance with medication, physical activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Assess patient &amp; family understanding of recommendations and rationale</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Identify barriers to adherence</td>
<td></td>
</tr>
</tbody>
</table>

### Nursing Implementation:
- Identify high-risk individuals (e.g., asthma, COPD) and those with cardiopulmonary symptoms prior to initiating immunotherapy. Establish a thorough baseline
- Educate patients that new pulmonary symptoms should be reported immediately
- Anticipate that the steroid requirements to manage pneumonitis are high (1–4 mg/kg/day) and patient will be on corticosteroid therapy for at least 1 month
- Educate patients and family about the rationale for discontinuation of immunotherapy in patients who do develop moderate or severe pneumonitis

### RED FLAGS:
- Risk of acute onset
- Risk of mortality if pneumonitis treatment is delayed
- Risk of pneumonitis is greater in patients receiving combination immunotherapy regimens

ADL = activities of daily living; COPD = chronic obstructive pulmonary disease

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Pneumonitis Page 2 of 2
## Care Step Pathway - Arthralgias and Arthritis

### Nursing Assessment

**Look:**
- Does the patient appear uncomfortable?
- Does the patient appear unwell?
- Is their gait affected?
- Obvious swollen, or deformed joint(s)?
- Is the patient having trouble getting up and down stairs?

**Listen:**
- Have symptoms worsened?
- Are symptoms limiting ADLs?
- Are symptoms increasing the patient’s risk for fall? Other safety issues?
- Associated symptoms?
  - Fatigue (new or worsening)

**Recognize:**
- Is there a pre-existing autoimmune dysfunction?
- Is there a history of prior orthopedic injury, DJD, OA, RA?
- Other immune-related adverse effects
- Three subtypes of inflammatory arthritis associated with checkpoint inhibitors:
  1. Polyarthritis similar to rheumatoid arthritis
  2. True reactive arthritis with conjunctivitis, urethritis, and oligoarthritis
  3. Subtype similar to seronegative spondyloarthritis with inflammatory back pain and predominantly larger joint involvement.

### Grading Toxicity

**Arthralgia**

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

<table>
<thead>
<tr>
<th>Grade 1 (Mild)</th>
<th>Grade 2 (Moderate)</th>
<th>Grade 3 (Severe)</th>
<th>Grade 4 (Potentially Life-Threatening)</th>
<th>Grade 5 (Death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild pain</td>
<td>Moderate pain; limiting instrumental ADL</td>
<td>Severe pain; limiting self-care ADL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Arthritis**

Definition: A disorder characterized by inflammation involving a joint

<table>
<thead>
<tr>
<th>Grade 1 (Mild)</th>
<th>Grade 2 (Moderate)</th>
<th>Grade 3 (Severe)</th>
<th>Grade 4 (Potentially Life-Threatening)</th>
<th>Grade 5 (Death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild pain with inflammation, erythema, or joint swelling</td>
<td>Moderate pain associated with signs of inflammation, erythema, or joint swelling; limiting instrumental ADL</td>
<td>Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self-care ADL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Management**

**Overall Strategy:**
- Assess for other etiologies, such as lytic or osseous metastasis
- Early intervention to maintain or improve physical function and impact on QOL; symptom control through the treatment of inflammation and pain is often achieved with NSAIDs, corticosteroids, and other adjunct therapies

---

**Prevention**
- No known interventions

**Grade 1 (Mild)**
- Anticipate immunotherapy to continue
- Encourage physical activity
  - 30 minutes of low-to-moderate-intensity physical activity 5 days per week can improve physical conditioning, sleep, and decreases pain perception
  - For physically inactive patients, advise supervised exercise, resistance training
  - Other: yoga, tai chi, Qigong, Pilates, aqua exercise, focused dance programs
- Anticipate use of analgesia
  - Low-dose NSAIDs
    - Topical: diclofenac (gel or patch). Best for localized, limited, superficial joint inflammation or for use in patients who cannot tolerate oral NSAIDs
    - Oral: ibuprofen, naproxen, celecoxib
  - Anticipatory guidance on proper administration
- Assess patient and family understanding of recommendations and rationale
  - Identify barriers to adherence

**Grade 2 (Moderate)**
- Ipilimumab to be withheld for any Grade 2 event (until Grade 0/1) and discontinued for events persisting ≥2 weeks or inability to reduce steroid dose to 7.5 mg prednisone or equivalent per day
- Dose of pembrolizumab or nivolumab to be held as to not make symptoms worse
- Pembrolizumab or nivolumab to be discontinued for Grade 2 events persisting ≥12 weeks
- Continue to encourage physical activity
  - Anticipate use of analgesia
    - NSAIDs
      - Oral: ibuprofen, naproxen, celecoxib
    - Anticipatory guidance on proper administration
- Anticipatory referral to rheumatology for collaborative management and consideration of adjunct treatment
- Anticipate pre-visit assessment: CBC, ESR, CRP, BUN/CR & aminotransferases, ANA, RF
  - Intraarticular steroids to be used for significant symptomatic joint(s)
  - Low-dose corticosteroids (0.5 – 1 mg/kg/day) to be used
    - Anticipatory guidance on proper administration
    - Duration of corticosteroid therapy is usually limited, lasting for about 4–6 weeks, with possible resolution of symptoms within weeks to months of treatment
- Assess patient & family understanding of toxicity, rationale for treatment hold (if applicable)
  - Identify barriers to adherence

**If symptoms do not improve in 4–6 weeks, escalate to next level of therapy**

**Grade 3-4 (Severe or Life-Threatening)**
- Pembrolizumab or nivolumab to be withheld for first-occurrence Grade 3/4 event and discontinued if:
  - Grade 3/4 event recurs
  - Persist ≥12 weeks
  - Ipilimumab to be discontinued for any Grade 3/4 event.
  - High-dose steroids to be used (1-1.5 mg/kg) daily; [rapid effect within days]
  - Anticipatory guidance on proper administration
  - Onset of action is rapid, typically within days
- Anticipatory referral to rheumatology for collaborative management and consideration of adjunct treatment
  - Non-biologic agents (more likely to be recommended)
    - Conventional synthetic DMARDs (csDMARDs), which have a delayed effect and take weeks to work:
      - Methotrexate
      - Sulfasalazine*
      - Hydroxychloroquine
      - Leflunomide
  - Biologic agents (less likely to be recommended)
    - Biologic DMARDs (bDMARDs)
    - TNF inhibitors
      - Infliximab
      - Etanercept
      - Adalimumab
      - Golimumab
      - Certolizumab pegol
    - Anti B-cell agents (CD-20 blocking)
      - Rituximab
  - Agents NOT advised
    - Interleukin (IL)-6 receptor blocking agent (tocilizumab) and JAK inhibitors (tofacitinib) due to risk of colonic perforation
    - T cell co-stimulation inhibitor (abatacept) as it directly opposes the mechanism of checkpoint blockade agents
- Assess patient & family understanding of toxicity and rationale for treatment discontinuation
  - Identify barriers to adherence, specifically compliance with medication, physical activity

* Sulfasalazine is associated with rash; do not use in patients with history of or current treatment-related dermatitis
Nursing Implementation:
- Identify high-risk individuals and those with underlying autoimmune dysfunction
- Educate patients that arthralgias and arthritis are the most commonly reported rheumatic and musculoskeletal irAEs with checkpoint inhibitors
- Arthritis-like symptoms can range from mild (managed well with NSAIDs and low dose corticosteroids) to severe and erosive (requiring multiple immunosuppressant medications)
- 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 symptoms can persist beyond treatment completion or discontinuation

RED FLAGS:
- Risk of fall due to mobility issue

ADLs = activities of daily living; ANA = antinuclear antibody; BUN = blood urea nitrogen; CBC = complete blood count; CR = creatinine; CRP = C-reactive protein; DJD = degenerative joint disease; DMARD = disease-modifying antirheumatic drug; ESR = erythrocyte sedimentation rate; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis; QOL = quality of life; RA = rheumatoid arthritis; RF = rheumatoid factor; TNF = tumor necrosis factor
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
- Paresthesia
- Laboratory values
- Does the patient have diabetes mellitus?
- Are there neurologic signs and symptoms?
- Results of prior imaging
  - Metastases to spinal cord
  - Other metastases that may cause symptoms

Grading of Neuropathy:

<table>
<thead>
<tr>
<th>Grade 1 (Mild)</th>
<th>Grade 2 (Moderate)</th>
<th>Grade 3 (Severe)</th>
<th>Grade 4 (Potentially Life-Threatening)</th>
<th>Grade 5 (Death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral Motor:</td>
<td>Moderate symptoms; limiting ADLs</td>
<td>Severe symptoms; limiting self-care ADLs, requires assistive devices</td>
<td>Life-threatening; urgent intervention indicated</td>
<td>Life-threatening; urgent intervention indicated</td>
</tr>
<tr>
<td>Peripheral Sensory: Asymptomatic; loss of deep tendon reflexes or paresthesia</td>
<td>Moderate symptoms; limiting ADLs</td>
<td>Severe symptoms; limiting self-care ADLs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Management

- 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
- Neurology consult
  - Consideration of electromyogram and nerve conduction tests
  - Immune globulin infusions
  - Plasmapheresis
- Taper steroids slowly over at least 4 weeks once symptoms improve
- If needed, obtain physical therapy or occupational therapy consult (for both functional assessment and evaluate safety of patient at home)
- Supportive medications for symptomatic management

Overall Strategy:
- 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
- Neurology consult
  - Consideration of electromyogram and nerve conduction tests
  - Immune globulin infusions
  - Plasmapheresis
- Taper steroids slowly over at least 4 weeks once symptoms improve
- If needed, obtain physical therapy or occupational therapy consult (for both functional assessment and evaluate safety of patient at home)
- Supportive medications for symptomatic management

Note: 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 medications 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. ADLs = activities of daily living.
Nursing Assessment:
- Does the patient appear weak?
- Does the patient appear uncomfortable?
- Altered ambulation or general movement?
- If muscular weakness is present, any respiratory difficulties apparent?

Grading of Neuropathy:
- 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
- Does the patient have diabetes mellitus?
- Are there neurologic signs and symptoms?
- Results of prior imaging
  - Metastases to spinal cord
  - Other metastases that may cause symptoms

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
- Neurology consult
  - Consideration of electromyelogram and nerve conduction tests
  - Immune globulin infusions
  - Plasmapheresis
- Taper steroids slowly over at least 4 weeks once symptoms improve
- If needed, obtain physical therapy or occupational therapy consult (for both functional assessment and evaluate safety of patient at home)
- Supportive medications for symptomatic management

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

Nursing Implementation:
- Compare baseline assessment; grade & document neuropathy and etiology (diabetic, medication, vascular, chemotherapy)
- Early identification and evaluation of patient symptoms
- Early intervention with lab work and office visit if neuropathy symptoms suspected

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 & 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

RED FLAGS:
- Guillain–Barré syndrome
- Myasthenia gravis

ADLs = activities of daily living
Care Step Pathway – Nephritis (inflammation of the kidneys)

Nursing Assessment

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

Listen:
- Has there been change in urination?
  - Urine color?
  - Frequency?
- How much fluid is the patient taking in?
- Are associated symptoms present?
  - Nausea?
  - Headache?
  - Malaise?
  - Lung edema?
- Are there symptoms concerning for:
  - Urinary tract infection?
  - Pyelonephritis?
  - Worsening CHF?
- Are symptoms limiting ADLs?
- Current or recent use of nephrotoxic medications (prescribed and OTC) other agents?
  - NSAIDs
  - Antibiotics
  - Contrast media or other nephrotoxic agents (contrast dye, aminoglycosides, PPI)?

Recognize:
- Laboratory abnormalities (elevated creatinine, electrolyte abnormalities)
- Urinalysis abnormalities (casts)
- Abdominal or pelvic disease that could be causing symptoms
- Prior history of renal compromise?
- Other immune-related adverse effects?
- Presence of current or prior immune-mediated toxicities, including rhabdomyolysis
- Is patient volume depleted?

Grading Toxicity

Acute Kidney Injury, Elevated Creatinine
Definition: A disorder characterized by the acute loss of renal function and is traditionally classified as pre-renal, renal, and post-renal.

<table>
<thead>
<tr>
<th>Grade 1 (Mild)</th>
<th>Grade 2 (Moderate)</th>
<th>Grade 3 (Severe)</th>
<th>Grade 4 (Potentially Life-Threatening)</th>
<th>Grade 5 (Death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine level &gt;0.3 mg/dL; creatinine 1.5–2× ULN</td>
<td>Creatinine 2–3× ULN</td>
<td>Creatinine &gt;3× ULN or &gt; 4.0 mg/dL; hospitalization indicated</td>
<td>Life-threatening consequences; dialysis indicated</td>
<td>-</td>
</tr>
</tbody>
</table>

Does the patient appear uncomfortable?
Does the patient look ill?
Has there been change in urination?
- Urine color?
- Frequency?
How much fluid is the patient taking in?
Are associated symptoms present?
- Nausea?
- Headache?
- Malaise?
- Lung edema?
Are there symptoms concerning for:
- Urinary tract infection?
- Pyelonephritis?
- Worsening CHF?
Are symptoms limiting ADLs?
Current or recent use of nephrotoxic medications (prescribed and OTC) other agents?
- NSAIDs
- Antibiotics
- Contrast media or other nephrotoxic agents (contrast dye, aminoglycosides, PPI)?
Laboratory abnormalities (elevated creatinine, electrolyte abnormalities)
Urinalysis abnormalities (casts)
Abdominal or pelvic disease that could be causing symptoms
Prior history of renal compromise?
Other immune-related adverse effects?
Presence of current or prior immune-mediated toxicities, including rhabdomyolysis
Is patient volume depleted?
Creatinine level >0.3 mg/dL; creatinine 1.5–2× ULN
Creatinine 2–3× ULN
Creatinine >3× ULN or > 4.0 mg/dL; hospitalization indicated
Life-threatening consequences; dialysis indicated
-
Management

**Overall Strategy**
- Assess for other etiologies, such as infection
- Eliminate potentially nephrotoxic medications
- Ensure adequate hydration daily
- Evaluate for progressive kidney/adrenal/pelvic metastases that may be contributing to kidney dysfunction
- Early intervention to maintain or improve physical function and impact on QOL

**Mild elevation in creatinine (Grade 1)**
- Anticipate immunotherapy to continue
- Perform detailed review of concomitant medications (prescribed and OTC), herbas, vitamins, anticipating possible discontinuation of nephrotoxic agents
- Avoid/minimize addition of nephrotoxic agents, such as contrast media for radiology tests
- Anticipate close monitoring of creatinine (i.e., weekly)
- Educate patient/family on importance of adequate daily hydration and set individualized hydration goals
- Review symptoms to watch for with patient and family and remember to assess at subsequent visits

**Moderate elevation in creatinine (Grade 2)**
- Ipilimumab to be withheld for any Grade 2 event (until Grade 0/1) and discontinued for events persisting ≥6 weeks or inability to reduce steroid dose to 7.5 mg prednisone/day
- Pembrolizumab or nivolumab to be withheld for Grade 2 events persisting ≥12 weeks or inability to reduce steroid dose to ≤10 mg prednisone or equivalent per day
- Anticipate increase in frequency of creatinine monitoring (i.e., every 2–3 days until improvement)
- Immunosuppressive medications to be initiated to treat immune-mediated nephritis
  - Systemic corticosteroids (e.g., prednisone) 0.5–1 mg/kg/day until symptom improve to baseline followed by slow taper over at least 1 month
  - Anticipate increased in corticosteroid dosing (i.e., treat as if Grade 3 nephritis) if creatinine does not improve within 48–72 hours
  - Anticipate use of additional supportive care medications
- Upon symptoms resolution to patient’s baseline, or Grade 1, begin to taper corticosteroid dose slowly over 1 month
- Anticipatory guidance on proper administration
- Anticipate the use of IV fluid to ensure adequate hydration
- Anticipate that nephrology consultation may be initiated by provider
- Assess patient & family understanding of recommendations and rationale
- Identify barriers to adherence

**Moderate (Grade 3) and Severe (Grade 4)**
- Pembrolizumab or nivolumab to be withheld for first-occurrence Grade 3/4 event and discontinued if:
  - Grade 3/4 event recurs
  - Persists ≥12 weeks
  - Requires >10 mg prednisone or equivalent per day for more than 12 weeks.
- Ipilimumab to be discontinued for any Grade 3/4 event
- Immunosuppressive medications to be initiated to treat immune-mediated nephritis
  - Corticosteroids (e.g., prednisone 1–2 mg/kg/day, in divided doses) until symptoms improve to baseline and then slow taper over at least 1 month
  - If symptoms do not improve within 48–72 hours, additional immunosuppressive medications will be considered
- Anticipate nephrology consultation will be initiated by provider
- Anticipate that renal biopsy will be considered
- Hemodialysis may be considered
- Anticipate possible hospital admission for Grade 4 elevations in creatinine or in patients with multiple comorbidities

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**DISCLAIMER:**
This information is for educational purposes only. It is not intended to replace the advice or care of a health provider. The Melanoma Nursing Initiative (MNI) strongly encourages consultation with a health provider for any clinical questions or concerns. The MNI does not provide medical advice, examination, or treatment. Medical advice should always be obtained from a health provider. The information on this page is not intended to diagnose or treat any medical condition. The MNI is not liable for any adverse outcomes resulting from any actions undertaken based on the information on this page.
Nursing Implementation:
- Identify individuals with pre-existing renal dysfunction prior to initiating immunotherapy. Ensure baseline creatinine has been obtained
- Check kidney function prior to each dose of immunotherapy
- Monitor creatinine more frequently if levels appear to be rising, and for Grade 1 toxicity
- Educate patients that new urinary symptoms should be reported immediately
- 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
- Educate patients and family about the rationale for discontinuation of immunotherapy in patients who develop severe nephritis

RED FLAGS:
- Risk of acute onset
- Risk of mortality if unrecognized or treatment is delayed
- Risk of immune-mediated nephritis is greater in patients receiving combination immunotherapy regimens and PD-1 inhibitors
- In addition to acute interstitial nephritis seen from PD-1 inhibitors, there are case reports of lupus-like nephritis and granulomatous acute interstitial nephritis

ADLs = activities of daily living; CHF = congestive heart failure; LE = lung edema; NSAIDs = nonsteroidal anti-inflammatory drugs; OTC = over the counter; PPI = proton pump inhibitor; QOL = quality of life; ULN = upper limit of normal.
APPENDIX 2
## Management of other AEs associated with pembrolizumab monotherapy

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Common symptoms</th>
<th>Common management/anticipatory guidance</th>
</tr>
</thead>
</table>
| 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 (seen with nivolumab, included here for completeness) | 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* |
## Management of other AEs associated with pembrolizumab monotherapy (Continued)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Common symptoms</th>
<th>Common management/anticipatory guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion reaction</td>
<td>Chills/shaking, back pain, itching, flushing, difficulty breathing, hypotension, fever</td>
<td>• Nivolumab and/or ipilimumab: For mild/moderate (Grade 1–2) reactions: interrupt or slow rate of infusion; monitor to recovery.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 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</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Difficulty falling or staying asleep</td>
<td>• Counsel patients on good sleep habits; prescription medications can be used if needed (Should improve over time)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Anticipate standard dose holds/discontinuations*</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>Vomiting, queasiness, RUQ or LUQ pain</td>
<td>• Standard supportive care is usually adequate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• May indicate hepatotoxicity; check LFTs/lipase/amylase</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Anticipate standard dose holds/discontinuations*</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>Cough, runny nose, sore throat, nasal breathing</td>
<td>• Evaluate potential causes—a dry cough and shortness of breath would increase concern for pneumonitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Standard supportive care</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Anticipate standard treatment holds*</td>
</tr>
</tbody>
</table>

*Withhold pembrolizumab 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.