Both nivolumab (Opdivo®) and ipilimumab (Yervoy®) are approved as monotherapies for the treatment of unresectable or metastatic (advanced) melanoma (discussed in separate nursing tools). They are also approved for use together as combination therapy in this patient population. Nivolumab and ipilimumab each improve anticancer responses and patient survival by inhibiting molecules known as checkpoints to enhance the patient’s immune response to melanoma. Nivolumab inhibits the checkpoint known as programmed death receptor-1 (PD-1), and ipilimumab inhibits the checkpoint cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4).

Antitumor activity is improved with nivolumab/ipilimumab combination therapy compared with either monotherapy, but the risk and severity of immune-related adverse events (irAEs) is also heightened.

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.
Obtain pretreatment laboratory tests (eg, adrenal function [ACTH], clinical chemistries, liver function tests, and thyroid function tests) prior to initiation of therapy and before each cycle.

**Nivolumab + Ipilimumab Regimen**

- The dosing schema for the induction and maintenance phases is shown below.
- Vials of nivolumab and ipilimumab should not be shaken.
- infusion bags and in-line filters with pore sizes of 0.2 – 1.2 microns for each infusion.
- When administered in combination with each other, nivolumab should be infused first, followed on the same day by ipilimumab, using separate infusion bags and in-line filters with each other.
- Nivolumab and ipilimumab are clear to opalescent, colorless to pale-yellow solutions.
- Both nivolumab and ipilimumab are monoclonal antibodies administered via intravenous infusion, using separate intravenous lines.
- Both nivolumab and ipilimumab are monoclonal antibodies administered via intravenous infusion, using separate intravenous lines.
- Both nivolumab and ipilimumab are monoclonal antibodies administered via intravenous infusion, using separate intravenous lines.
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### SIDE EFFECTS AND THEIR MANAGEMENT

Because nivolumab and ipilimumab are immunotherapies that work by enhancing the patient’s immune system, most adverse reactions associated with the combination are related to overactivity of the patient’s immune system (i.e., immune-related adverse events [irAEs]). Various organ systems or tissues may be affected. Risk and severity of irAEs are relatively higher when nivolumab and ipilimumab are coadministered than when used as monotherapies. The irAEs associated with nivolumab/ipilimumab combination therapy also tend to have an earlier onset.

- **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)
  - Nivolumab/ipilimumab will likely be held or discontinued depending on severity and/or persistence of the irAE
  - Referral to organ specialist should be considered

- irAEs associated with nivolumab/ipilimumab combination therapy can be categorized as 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/ipilimumab are shown in Appendix 2

### Table 1. List of Care Step Pathways for the management of immune-related AEs associated with nivolumab/ipilimumab therapy

<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)</td>
<td>Appendix 1</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal toxicities</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- 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></td>
<td>- Elevated transaminases</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</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

• Nivolumab/ipilimumab-related irAEs may occur at any time, including after treatment completion or discontinuation. Continuing to monitor patients is critical.

• 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.

• 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/ipilimumab regimen with them at all times. This might be the nivolumab- and ipilimumab-specific wallet cards or at least emergency phone numbers and the side effects associated with the regimen. You may suggest 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. After a well-tolerated induction with combination nivolumab/ipilimumab, a patient does well and has a significant response. The patient also does well on maintenance for a year, with stable disease, but then the disease begins to progress. Can the patient be reinduced with nivolumab/ipilimumab?

A. Reinduction can be a reasonable consideration. Evaluation for a clinical trial should always be taken into consideration when contemplating a change in therapy. Reintroduction with a single-agent immunotherapy is also an option.

Q. Should an asymptomatic endocrinopathy be treated?

A. A transient period of asymptomatic hyperthyroidism can sometimes be observed with PD-1 monotherapy, but it is more commonly observed early in treatment with combination nivolumab/ipilimumab. In the Checkmate 067 phase 3 trial, 15% of patients treated with the combination experienced hypothyroidism of any grade (Larkin J et al. N Engl J Med. 2015; 373:23-34).

This period is typically followed by hypothyroidism which can be clinically detectable and often requires permanent hormone replacement therapy.

Q. If it is not possible (because of side effects) for a highly motivated patient to complete all 4 induction cycles of combination nivolumab/ipilimumab, is it considered incomplete treatment or a “failure” to achieve a full course?

A. Goals of therapy are always geared toward safely adhering to the treatment plan regimen. Not all patients are able to complete all 4 induction infusions because of side effects. This is not deemed as a failure, as every patient responds to immune stimulation differently and not all patients can safely tolerate all 4 cycles.

Benefits have been observed with patients who did not complete all 4 induction cycles. In the phase 2 study, 68% of patients in a phase 2 trial who did not complete the induction regimen with nivolumab/ipilimumab had objective responses (Postow MA et al. N Engl J Med. 2015; 2006-2017). These data show that it is possible to have a therapeutic immune response with less than 4 cycles of induction.
Q. If a patient does not finish all 4 doses of induction, can they go on to receive maintenance nivolumab?

A. This decision is made on an individual basis. Some safety factors taken into consideration are: (1) the severity of immune related side effects; (2) the time it took for the side effects to resolve; and (3) the specific side effects that contributed to the truncation of induction. Oftentimes, patients have been able to successfully transition to maintenance nivolumab.
Financial Assistance
BMS Access Support
1 (800) 861-0048
http://www.bmsaccesssupport.bmscustomerconnect.com/patient

Additional Patient Resources
For more information about this therapy and support:
Guide to Opdivo/Yervoy Combination Treatment
https://www.opdivo.com/servlet/servlet.FileDownload?file=00Pi0000000a9ZEAQ

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

- Food and Drug Administration & Bristol-Myers Squibb. Risk Evaluation and Mitigation Strategy (REMS) for ipilimumab (Yervoy); February 2012. Includes wallet card etc. Available at: https://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM249435.pdf


APPENDIX 1
Skin Toxicities

**RED FLAGS:**

- Immediate barriers to adherence
- Identify barriers to adherence
- Specifically compliance with steroids when transitioned to oral corticosteroids
- Identify barriers to adherence
- Monitor vigilantly. Instruct patient & advise strict sun protection
- For sleep
- Keep fingernails short
- Rationale for hospitalization and intervention indicated
- Rationale for discontinuation of treatment
- Risk of opportunistic infection and need for antibiotic prophylaxis
- Contraindication to continue
- Oral antihistamines will be used in some patients
- Risk to life (threatening)
- Grade 4 (Severe or Life-Threatening)

**Management**

**Assessment:**

- Intense or widespread; constant; limiting self-care ADL or sleep
- Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); limiting instrumental ADLs
- Mild or localized; topical treatment may be effective

**Intervention in at-risk patients:**

- Antihistamines will be used in some patients
- Risk to life (threatening)
- Grade 4 (Severe or Life-Threatening)

**Overall Strategy**

- Consider dermatology consult +/- biopsy
- Anticipate dermatology consult +/- biopsy
- Pembrolizumab or nivolumab to be used
- Ipilimumab to be discontinued for any Grade 3/4 event that recurs, persists
- Nivolumab to be withheld for Grade 3 rash or confirmed SJN or TEN
- Grade 5 (Death)
- Monitor ADLs & body surface area
- SJN = Stevens-Johnson syndrome; TEN = Toxic epidermal necrolysis

**Grade 1 (Mild)**

- Advise vigilant skin care
- Cool cloth applications
- H2 blocker
- Astringent, such as menthol or camphor

**Grade 2 (Moderate)**

- Advice strict sun protection
- Antimicrobial prophylaxis
- Avoid rigid skin care
- Cool cloth applications
- Tepid baths; oatmeal baths
- Antihistamines
- Monitor vigilantly

**Grade 3 (Severe)**

- Advice strict sun protection
- Antibiotic prophylaxis
- Consider dermatology consult
- Tepid baths; oatmeal baths
- Antihistamines
- Moisturizers containing humectants (urea, glycerin)
- Tepid baths; oatmeal baths
- Immerse in tepid water

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

- Hospitalization & intervention indicated
- Antihistamines
- Antibiotic prophylaxis
- Consider dermatology consult
- Immune modulators, monoclonal antibodies, chemotherapy, surgery, radiation therapy

**Grade 5 (Death)**

- Hospitalization & intervention indicated
- Antihistamines
- Antibiotic prophylaxis
- Consider dermatology consult
- Immune modulators, monoclonal antibodies, chemotherapy, surgery, radiation therapy

**Pruritus**

- A disorder characterized by an intense itching sensation

**MACULOPAPULAR RASH**

- A disorder characterized by the presence of macules (flat) and papules (elevated); frequently affecting the upper trunk, spreading centripetally and associated with pruritus, burning, tightness)

**Definition:**

- Macules/papules covering <10% BSA with or without symptoms
- Macules/papules covering 10-30% BSA with or without symptoms and associated with superinfection requiring IV antibiotics
- Papules/pustules covering any % BSA with or without symptoms and associated with superinfection requiring IV antibiotics

**Grading Toxicity**

- Grade 1 (Mild)
- Grade 2 (Moderate)
- Grade 3 (Severe)
- Grade 4 (Potentially Life-Threatening)
- Grade 5 (Death)

**Overall Strategy**

- Consider dermatology consult
- Antimicrobial prophylaxis
- Consider dermatology consult
- Immune modulators, monoclonal antibodies, chemotherapy, surgery, radiation therapy

**Intervention in at-risk patients:**

- Advice to patients about new medications, vitamins, supplements, alternative/complementary therapies, etc.
- Assess for other etiology of rash; ask patient about new medications, vitamins, supplements, alternative/complementary therapies, etc.

**Nursing Assessment**

- Look:
  - Are symptoms interfering with ADLs?
  - Does the patient appear uncomfortable?
  - Does the patient appear unwell?
  - Are skin changes?
  - Is there an obvious rash?
  - Are symptoms interfering with ADLs?

- Listen:
  - Does the patient appear uncomfortable? (e.g., pruritus, burning, tightness)
  - Is there an obvious rash?
### Gastrointestinal Toxicity - Diarrhea and Colitis

#### Grading Toxicity

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Mild)</td>
<td>Indicated: patient's bowel habits; medical intervention indicated.</td>
</tr>
<tr>
<td>2 (Moderate)</td>
<td>Moderate increase of output in baseline; incontinence.</td>
</tr>
<tr>
<td>3 (Severe)</td>
<td>Severe increase of output compared with baseline.</td>
</tr>
<tr>
<td>4 (Potentially Life-Threatening)</td>
<td>Life-threatening (e.g., perforation, bleeding).</td>
</tr>
<tr>
<td>5 (Death)</td>
<td>Death</td>
</tr>
</tbody>
</table>

### Care Step Pathway - Gastrointestinal Toxicity: Diarrhea and Colitis

#### Nursing Assessment

**Listen:**
- Does the patient appear in distress?
- Does the patient appear dehydrated?

**Look:**
- Does the patient appear weak?
- Does the patient appear pale?

**Recognize:**
- Fever
- Diarrhea, dark or bloody stools
- Bloating/increased gas
- Nausea, vomiting
- Decreased appetite or food aversions
- Pain, tenderness, bloating
- Fluid and electrolyte abnormalities

**Recognize (including Anticipatory Guidance):**
- Dehydrated
- Acute change in bowel habits
- Change in color, consistency of stools
- Change in frequency of stools
- Change in fluid intake and output
- Change in energy level

#### Care Plan

**Care Plan:**

1. **Dehydration Management**
   - Monitor fluid intake and output.
   - Administer intravenous fluids as needed.

2. **Nutritional Support**
   - Provide high-calorie, high-protein meals.
   - Monitor for food aversions.

3. **Gastrointestinal Support**
   - Administer anti-diarrheal medications as prescribed.
   - Monitor for side effects.

4. **Surgical Consultation**
   - Evaluate for surgical consultation for complications.

5. **Immunotherapy Management**
   - Monitor for immunotherapy-related adverse events.
   - Discontinue immunotherapy as necessary.

6. **Laboratory Monitoring**
   - Monitor for serum chemistry/hematology abnormalities.

7. **Symptom Management**
   - Manage symptoms with non-pharmacological interventions.

8. **Consultation with Other Healthcare Professionals**
   - Consult with GI specialists as needed.

**Notes:**

- Tapershould consider patient's current symptom profile.
- Steroid taper instructions/calendar as a guide but not an absolute.
- Early intervention with lab work and office visit if colitis symptoms are suspected.
- Early identification and evaluation of patient symptoms.

### Other Considerations

- Anti-acid therapy daily as gastric ulcer prevention while on steroids.
- Be alert to recurring symptoms as steroids taper down and report them (taper may need to be adjusted).
- Avoid alcohol/acetaminophen or other hepatoxins.
- Consider additional antiviral and antifungal coverage.
- Decrease fiber, uncooked fruit and vegetables, red meats, dairy, oil, caffeine, alcohol, sugar.
- Use caution with analgesics (opioids) and anti-diarrheal medications.
- Avoid laxatives or stool softeners.
- Infections caused by Clostridium difficile.
- Send stool sample for C difficile testing.
- （Including immune-related adverse events）
- （Severe or Life-Threatening）
- （Severe）
- （Moderate）
- （Mild）
- （Death）
Fever
- More frequent stools, consistency change from loose to liquid
- Change in gastrointestinal function, decreased appetite

**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)

**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

**Taper should consider patient’s current symptom profile**

- Early intervention with lab work and office visit if colitis symptoms are suspected
- Early identification and evaluation of patient symptoms
- **Compare baseline assessment:** grade & document bowel frequency

**Grade 1 (Mild):**
- Diarrhea (increased frequency, loose, large volume, or liquid stools)
- Decreased appetite or food aversions
- Increased fatigue
- Serum chemistry/hematology abnormalities
- Peritoneal signs of bowel perforation (i.e., tenderness, pain, tenderness, bloating)
- Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs collapse); urgent intervention indicated

**Grade 2 (Moderate):**
- Fever
- Moderate diarrhea is more likely when treatment is resumed

- Common symptoms of 2- to 7-week steroids:
- Fever
- Diarrhea
- Malaise
- Pain
- Nausea

**Dehydration is a side effect of steroids & is a concern**

- Consider gastroenterology consult for possible intervention

**Management (Including Anticipatory Guidance):**

**Overall Strategy:**
- Rule out infections, non-infectious, disease-related etiologies
- May continue immunotherapy

**Gastrointestinal Toxicity:**

**Supportive medication for symptomatic management:**
- Continuation of medications used to treat baseline symptoms
- Vomiting with or without diarrhea
- Vomiting with nausea
- Pain
- Tiredness

**Side effects to be expected over 2 to 4 weeks:**
- Nausea
- Vomiting
- Diarrhea
- Fever
- Malaise
- Pain

**Side effects to be expected over 2 to 6 weeks:**
- Fever
- Malaise
- Pain
- Nausea

**Side effects to be expected over 6 to 12 weeks:**
- Fever
- Malaise
- Pain
- Nausea

**Common symptoms of 2- to 7-week steroids:**
- Fever
- Diarrhea
- Malaise
- Pain
- Nausea

**Early identification and evaluation of patient symptoms**

- **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)

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**Grade 2 (Moderate):**
- Fever
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- Common symptoms of 2- to 7-week steroids:
- Fever
- Diarrhea
- Malaise
- Pain
- Nausea

**Dehydration is a side effect of steroids & is a concern**

- Consider gastroenterology consult for possible intervention

**Management (Including Anticipatory Guidance):**

**Overall Strategy:**
- Rule out infections, non-infectious, disease-related etiologies
- May continue immunotherapy

**Gastrointestinal Toxicity:**

**Supportive medication for symptomatic management:**
- Continuation of medications used to treat baseline symptoms
- Vomiting with or without diarrhea
- Vomiting with nausea
- Pain
- Tiredness

**Side effects to be expected over 2 to 4 weeks:**
- Nausea
- Vomiting
- Diarrhea
- Fever
- Malaise
- Pain
- Nausea

**Side effects to be expected over 2 to 6 weeks:**
- Fever
- Malaise
- Pain
- Nausea

**Side effects to be expected over 6 to 12 weeks:**
- Fever
- Malaise
- Pain
- Nausea

**Common symptoms of 2- to 7-week steroids:**
- Fever
- Diarrhea
- Malaise
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- Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs collapse); urgent intervention indicated

**Grade 2 (Moderate):**
- Fever
- Moderate diarrhea is more likely when treatment is resumed

- Common symptoms of 2- to 7-week steroids:
- Fever
- Diarrhea
- Malaise
- Pain
- Nausea

**Dehydration is a side effect of steroids & is a concern**

- Consider gastroenterology consult for possible intervention

**Management (Including Anticipatory Guidance):**

**Overall Strategy:**
- Rule out infections, non-infectious, disease-related etiologies
- May continue immunotherapy

**Gastrointestinal Toxicity:**

**Supportive medication for symptomatic management:**
- Continuation of medications used to treat baseline symptoms
- Vomiting with or without diarrhea
- Vomiting with nausea
- Pain
- Tiredness

**Side effects to be expected over 2 to 4 weeks:**
- Nausea
- Vomiting
- Diarrhea
- Fever
- Malaise
- Pain
- Nausea

**Side effects to be expected over 2 to 6 weeks:**
- Fever
- Malaise
- Pain
- Nausea

**Side effects to be expected over 6 to 12 weeks:**
- Fever
- Malaise
- Pain
- Nausea

**Common symptoms of 2- to 7-week steroids:**
- Fever
- Diarrhea
- Malaise
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**Early identification and evaluation of patient symptoms**

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- Fever
- Moderate diarrhea is more likely when treatment is resumed

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- Fever
- Diarrhea
- Malaise
- Pain
- Nausea

**Dehydration is a side effect of steroids & is a concern**

- Consider gastroenterology consult for possible intervention

**Management (Including Anticipatory Guidance):**

**Overall Strategy:**
- Rule out infections, non-infectious, disease-related etiologies
- May continue immunotherapy
Gastrointestinal Toxicity Page 3 of 3

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Programmed cell death protein 1

PD = activities of daily living; ADL

Bloating, nausea

Consider additional antiviral and antifungal coverage (daily)

Consider antimicrobial prophylaxis (sulfamethoxazole/trimethoprim double dose M/W/F; single dose if used daily)

Change in gastrointestinal function, decreased appetite

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, irritable, euphoric, manic), increased appetite, interrupted sleep, oral thrush, fluid retention

Anti-acid therapy daily as gastric ulcer prevention while on steroids

Close follow-up in person or by phone, based on individual need & symptomatology

Tapers should consider patient's current symptom profile

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

Early intervention with lab work and office visit if colitis symptoms are suspected

Grade symptom & determine level of care and interventions required

Early identification and evaluation of patient symptoms

Compare baseline assessment; grade & document bowel frequency

Nursing Implementation:

- Fever
- Abdominal pain
- More frequent stools, consistency change from loose to liquid
- Bloating/rule out nausea
- Change in gastrointestinal function, decreased appetite

Red Flags:

- Airway: Is the airway clear?
- Breathing: Are there signs of respiratory distress?
- Circulation: Is the patient alert and responsive?
- Disability:

Does the patient appear in distress?

Does the patient appear dehydrated?

Listen:

Serum chemistry/hematology abnormalities

Recognize:

Increased fatigue

Look:

Decreased appetite or food aversions

Limiting self-care ADLs

Serum chemistry/hematology abnormalities

Care Step Pathway

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

Diet modification:

- May continue immunotherapy
- Infliximab infusion delay may have life-threatening consequences
- Avoid laxatives or stool softeners
- 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, irritable, euphoric, manic), increased appetite, interrupted sleep, oral thrush, fluid retention
- Anti-acid therapy daily as gastric ulcer prevention while on steroids
- Close follow-up in person or by phone, based on individual need & symptomatology
Monitor hydration status

- Dexamethasone oral solution
- Corticosteroid rinses
  - simethicone
  - diphenhydramine/lidocaine/
  - "Miracle Mouthwash":
    - 0.5% doxepin mouthwash
    - 2% viscous lidocaine applied to
      lesions 15 minutes prior to meals
      - 0.5 tsp salt and 2 tbsps sodium bicarbonate rinses
- Analgesics
  - Anticipatory guidance regarding use of pharmacologic agents (as applicable)
    - Encourage sips of cool water or crushed ice
    - ½ tsp salt and 2 tbsps sodium bicarbonate rinses
- Increase frequency of brushing to Q4

Mucositis:
- Cevimeline HCI
- Pilocarpine

Identify barriers to adherence

- Pharmacologic
  - Natural lemon
  - Sugarless hard candies
  - Oral lubricants
    - Synthetic saliva

- Nonpharmacologic
  - Systemic opioids may be indicated
  - Analgesics
    - Advise secretagogues
      - Pharmacologic agents
    - Oral lubricants
      - Synthetic saliva

- Parenteral

Pharmacologic Agents Associated with Xerostomia
- Probiotics with Lactobacillus
- Benzydamine HCI

Assess patient & family understanding of toxicity

- Sugarless gum

Assess patient & family understanding of prevention strategies and rationale

- Unclear role of systemic corticosteroids
- Anticipate hospitalization if unable to tolerate oral solids or liquids
- Recurrent Grade 3 event (pembrolizumab, nivolumab)
- Ipilimumab to be withheld for any Grade 2 event persisting ≥ 12 weeks
- Nivolumab to be withheld for first occurrence
- Pembrolizumab to be withheld for first occurrence

Overall Strategy

- Anticipate need for supplemental nutrition

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

Xerostomia (Dry Mouth)

- Grade 5 (Death)
  - Severe pain; interfering with oral intake; modified diet indicated with oral intake; modified diet indicated
  - Inability to adequately aliment
  - Inability to adequately aliment
  - Tube feeding or total parenteral nutrition indicated; tube feeding or total parenteral nutrition indicated
  - Unstimulated saliva < 0.1 mL/min
  - Unstimulated saliva 0.1 to 0.2 mL/min

- Grade 4 (Potentially Life Threatening)
  - Severe pain; interfering with oral intake; modified diet indicated with oral intake; modified diet indicated
  - Tube feeding or total parenteral nutrition indicated; tube feeding or total parenteral nutrition indicated
  - Unstimulated saliva 0.1 to 0.2 mL/min

- Grade 3 (Severe)
  - Severe pain; interfering with oral intake; modified diet indicated
  - Tube feeding or total parenteral nutrition indicated; tube feeding or total parenteral nutrition indicated
  - Unstimulated saliva 0.1 to 0.2 mL/min

- Grade 2 (Moderate)
  - Moderate pain; not interfering with oral intake; unstimulated saliva 0.1 to 0.2 mL/min

- Grade 1 (Mild)
  - Asymptomatic or mild symptoms; unstimulated saliva >0.2 mL/min

- Grade 0 (Normal)
  - Unstimulated saliva >0.2 mL/min

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

Nursing Assessment

Care Step Pathway - Mucositis & Xerostomia

- Have symptoms worsened?
  - Exertion
    - Need for dental work (e.g., root canal, tooth extraction)
    - Recent dental/medical issues
    - Waking during the sleep to sip water
    - Difficulty eating
    - Mouth soreness
  - Mouth pain (tongue, gums, buccal mucosa)
  - A history of mouth sores

- Does the patient have thrush?
  - Look:
    - Does the patient appear unwell?
    - Does the patient appear dehydrated?
    - Licking lips to moisten mouth
    - Difficulty breathing
    - Loss of appetite

- Does the patient appear unwell?
  - Look:
    - Does the patient appear unwell?
Monitor hydration status
- Monitor weight

Dexamethasone oral solution

- Corticosteroid rinses
  - "Miracle Mouthwash":
  - 2% morphine mouthwash
  - 2% viscous lidocaine applied to lesions 15 minutes prior to meals
  - Gelclair®, Zilactin®

- Analgesics
  - Anticipatory 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
  - ½ tsp salt and 2 tbspsodium or
  - 1 tsp baking soda in 8 ounces of water
  - If unable to tolerate brushing, advise chlorhexidine gluconate 0.12% or sodium
  - Increase frequency of brushing to Q4
  - Vigilant oral hygiene

- Mucositis:
  - Cevimeline HCI
  - Pilocarpine

- Xerostomia:
  - Anticipatory guidance regarding use of pharmacologic agents (as applicable)
  - Oral lubricants
  - Sugarless hard candies
  - Systemic opioids may be indicated
  - Advise secretagogues
  - Synthetic saliva
  - Benzydamine HCI
  - Probiotics with sulfate mouthwash
  - Zinc supplements or 0.2% zinc
  - Probiotics with alcohol

- Overall Strategy
  - Review baseline intake
  - Assess patient & family current intake
  - Assess oral intake
  - Assess nutritional status
  - Underlying cause
  - Define unstimulated saliva flow (e.g., unstimulated saliva <0.1 mL/min)
  - Severe pain; interfering with oral intake; tube feeding or total parenteral nutrition indicated; urgent intervention indicated
  - Severe pain; interfering with oral intake
  - Inability to adequately aliment (e.g., copious water, saliva) without significant dietary alteration; unstimulated saliva flow ≥0.2 mL/min
  - Unstimulated saliva flow ≥0.2 mL/min
  - Grade 1 (Mild)
  - Asymptomatic or mild symptoms; no dietary or treatment alteration required
  - Grade 2 (Moderate)
  - Grade 3 (Severe)
  - Grade 4 (Potentially Life Threatening)
  - Death

Mucositis: Xerostomia

(Grading Toxicity)

Have symptoms worsened?
- Has patient’s medication been changed?
- Recognize:
  - Look:
    - Does the patient have thrush?
    - Does the patient appear dehydrated?
    - Does the patient appear uncomfortable?
    - Waking during the sleep to sip water
    - Licking lips to moisten often?
    - Any signs of dehydration on examination?
  - Listen:
    - Does the patient smoke?
    - Concomitant medications associated with causing dry mouth?
    - Does the patient appear unwell?
    - Other reports of dry membranes (e.g., eyes, nasal passages, vagina)
    - Reports of dry mouth often accompany mucositis
    - Other reports of dry membranes
    - A history of mouth sores
    - Other reports of dry membranes (e.g., eyes, nasal passages, vagina)
  - Ask:
    - Other reports of dry membranes
    - A history of mouth sores
    - Other reports of dry membranes
    - Other reports of dry membranes
    - Other reports of dry membranes
    - Other reports of dry membranes
  - Ask the patient about new medications (particularly antihistamines), herbals, supplements, alternative/complementary therapies
  - Ask the patient to explain their symptoms and understand the rationale for interventions as well as treatment discontinuation
  - Assess for other etiology of mucositis or dry mouth: candidiasis

Management (Including anticipatory guidance)

- Identify barriers to adherence
  - Pharmacologic and rationale for interventions as well as treatment discontinuation
  - Advise moistening agents
  - Dental referral if necessary

- Treatment for Mucositis
  - Mucositis
  - Nivolumab
  - Pembrolizumab
  - Ipilimumab
  - Discontinue for Grade 2 events persisting ≥12 weeks

- Treatment for Xerostomia
  - Nivolumab
  - Pembrolizumab
  - Ipilimumab
  - Discontinue for Grade 2 events persisting ≥12 weeks
**Nursing Assessment**

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

### 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>
</tr>
</thead>
<tbody>
<tr>
<td>AST/ALT ≥ 2× ULN</td>
<td>AST/ALT ≥ 3× ULN</td>
<td>AST/ALT ≥ 5× ULN</td>
<td>AST/ALT &gt; 10× ULN</td>
</tr>
<tr>
<td>Bilirubin: &gt; ULN–1.5× ULN</td>
<td>Bilirubin: &gt;1.5×–3.0× ULN</td>
<td>Bilirubin: &gt;3.0×–6.0× ULN</td>
<td>Bilirubin: &gt;6.0× ULN</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td><strong>Symptoms</strong></td>
<td><strong>Symptoms</strong></td>
<td><strong>Symptoms</strong></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Severe abdominal pain, ascites, somnolence, jaundice, mental status changes</td>
<td>Severe abdominal pain, ascites, somnolence, jaundice, mental status changes</td>
<td>Severe abdominal pain, ascites, somnolence, jaundice, mental status changes</td>
</tr>
<tr>
<td>Gastrointestinal distress</td>
<td>Gastrointestinal distress</td>
<td>Gastrointestinal distress</td>
<td>Gastrointestinal distress</td>
</tr>
<tr>
<td>Change in stool color (paler)</td>
<td>Change in stool color (paler)</td>
<td>Change in stool color (paler)</td>
<td>Change in stool color (paler)</td>
</tr>
<tr>
<td>Change in urine color (darker)</td>
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<td>Change in urine color (darker)</td>
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<tr>
<td>Change in energy level</td>
<td>Change in energy level</td>
<td>Change in energy level</td>
<td>Change in energy level</td>
</tr>
</tbody>
</table>

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**Recognize:**

- Does the patient appear acutely ill?
- Does the patient appear in acute distress?
- Are there any new findings?
- Have the patient's symptoms changed?
- Has the patient had any recent surgical procedures?
- Has the patient been prescribed any new medications?

**Look:**

- Does the patient have a fever?
- Does the patient have jaundice?
- Does the patient have ascites?
- Does the patient have abnormal liver function tests?
- Does the patient have abdominal pain?
- Does the patient have change in mental status?
- Does the patient have change in urine color?
- Does the patient have change in stool color?
- Does the patient have change in skin color?

---

**Overall Strategy:**

- **Initial Investigation:**
  - 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.
  - LFTs should be checked and results reviewed prior to each dose of immunotherapy.

- **Treatment:**
  - Steroids* to be initiated at 2mg/kg/day.
  - For Grade 1 or 2 events:
    - For Grade 1 event:
      - If LFTs normalized and symptoms resolved, steroids* to be tapered.
      - If LFTs stabilized or decreasing, continue steroid dosage.
    - For Grade 2 event:
      - If LFTs normalized and symptoms resolved, steroids* to be tapered.
      - If LFTs stabilized or decreasing, continue steroid dosage.
  - For Grade 3 or 4 events:
    - If LFTs normalized and symptoms resolved, steroids* to be tapered.
    - If LFTs stabilized or decreasing, continue steroid dosage.
    - Consider hospital admission for IV steroid regimen.
    - Consider antithymocyte globulin infusion.
    - Consider starting cellcept® (mycophenolate mofetil) 500mg.

- **Supportive Care:**
  - Anti-acid therapy daily as gastric ulcer prevention while on steroids.
  - Close follow-up in person or by phone, based on individual need and symptomatology.
  - Grade LFTs and any other accompanying symptoms.
  - Early intervention with lab work and office visit if hepatotoxicity is suspected.

---

**Hepatology/Gastroenterology Consult:**

- Once patient returns to baseline or Grade 4 steroids* to be tapered.
- If LFTs normalized and symptoms resolved, steroids* to be tapered.
- If LFTs stabilized or decreasing, continue steroid dosage.
- Consider starting cellcept® (mycophenolate mofetil) 500mg.
- Consider hospital admission for IV steroid regimen.
- Immunotherapy to be withheld if LFTs are trending upward; recheck LFTs within 1 week.
- Immunotherapy may be re-started at a reduced dose.

---

**Immunotherapy Discontinuation:**

- Immunotherapy to be discontinued for any recurrent Grade 3 event, and nivolumab or pembrolizumab for any recurrent Grade 3 event persisting.
- Pembrolizumab may be re-started at a reduced dose for any recurrent Grade 3 event.
- Nivolumab to be withheld for first occurrence of Grade 3 event.
- Recheck LFTs daily x 3 days or every 3 days; to be decreased LFT checks to q3 days, then weekly.
- LFTs daily x 3 days or every 3 days; to be decreased LFT checks to q3 days, then weekly.

---

**Non-Immuno Therapy Management:**

- Corticosteroids as primary treatment for mild to moderate hepatotoxicity.
- For severe hepatotoxicity, consider hospital admission for IV steroid regimen.
- For refractory to steroids potential for adding to steroid regimen.
- Consider hospital admission for IV steroid regimen.
- Hepatology/gastroenterology consult.
- If sustained elevation is significant and/or refractory to steroids potential for adding to steroid regimen.
- Immunotherapy to be withheld if LFTs are trending upward; recheck LFTs within 1 week.
- Infliximab infusions are not recommended due to potential hepatotoxic effects and other hepatotoxic meds, or supplements/herbals.
- Recreational substances (alcohol).
- Consider disease progression.
- Does the patient have any ascites?
- Does the patient appear jaundiced?
- Does the patient appear fatigued or listless?
- Does the patient have any change in mental status?
- Does the patient have any change in stool color (paler)?
- Does the patient have any change in urine color (darker)?
- Does the patient have any alteration in GI function?
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
- If LFT normalized and symptoms resolved, weekly days: decrease LFT checks to q3 days, then daily
- If LFTs stable/declining daily for 5 consecutive weeks when function recovers
- Grade 4 event. Ipilimumab to be discontinued
- Admission for IV steroids* to be initiated at 2mg/kg/day
- Consider hospital admission for IV steroids*
- Consider starting steroids* 0.5mg–1mg/kg/day
- Consider initiating immunosuppressive agents
- Steroids to be initiated at 2mg/kg/day
- Consider immunotherapy; recheck LFTs
- Consider liver biopsy
- Once patient returns to baseline or Grade 0–1, consider resuming treatment
- Steroid regimen immunosuppressive agent:
  - CellCept® (mycophenolate mofetil) 500 mg-1000mg po or IV q 12 hours
  - Antithymocyte globulin infusion
  - Infliximab infusions are not recommended due to potential hepatotoxic effects
  - Rule out infections (non-infectious); consider assessing for new onset or re-activation of viral infections, medications (acetaminophen, statins, corticosteroids), and other hematologic meds, or supplements/herbals)

Overall Strategy:

Management (including antibiotic guidance):
Avoid alcohol/acetaminophen or other hepatotoxins

Consider additional antiviral and antifungal coverage

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, hypomanic, euphoric, mania), increased appetite, interrupted sleep, oral thrush, fluid retention

Anti-acid therapy daily as gastric ulcer prevention while on steroids

Close follow-up in person or by phone, based on individual need & symptomatology

*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 intervention and evaluation of patient symptoms

Review LFT results prior to administration of immunotherapy

Nursing Implementation:

4 weeks over ≥ 6 weeks

If LFT normalized and symptoms resolved, weekly days: decrease LFT checks to q3 days, then weeks

Once patient returns to baseline or Grade 4

Antithymocyte globulin infusion q3 days, then weekly

If LFTs normalized and symptoms resolved, Consider hospital admission for IV methylprednisolone 125mg total daily

Consider liver biopsy

If sustained elevation and refractory to steroids*, potential for adding to regimen:
- CellCept® (mycophenolate mofetil) 500mg daily or for inability to reduce steroid dose to prednisone or equivalent daily oral
- Immunotherapy to be discontinued for任何 Grade 3 event, and nivolumab or pembrolizumab for any recurrent Grade 3 event
- Adenovirus reactivation

Threatening:
- Life-threatening:

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

Rule out infectious, non-infectious, and malignant causes. Consider assessing for new onset or re-activation of viral hepatitis, medications (acetaminophen, statins, LFTs should be checked and results reviewed prior to each dose of immunotherapy

Overall Strategy:

Bilirubin:
- >3.0×ULN
- >1.5×–3.0×ULN
- >3.0×–5.0×ULN
- >5.0×–20.0×ULN
- >20.0×ULN

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

Increased sweating?

Change in mental status?

Symptoms such as abdominal pain, ascites, o other symptoms such as abdominal pain, ascites, o other

Does the patient have any ascites?

Does the patient appear diaphoretic?

Does the patient appear fatigued or listless?

Change in skin color? Yellowing?

Change in energy level?

Listen:

Does the patient have any ascites?

Look:

Fevers?

Does the patient appear fatigued or listless?

Change in mental status?

Change in skin color? Yellowing?

Change in energy level?
Hypophysitis Page 1 of 2

Nursing Assessment

Care Step Pathway – Hypophysitis (Inflammation of the pituitary gland)

**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
- Secondary hypothyroidism: low free T4 and high TSH
- Secondary hypoadrenalism: low cortisol and high ACTH

**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 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 hydrocortisone 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).

**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.**

**RED FLAGS:**
- Symptoms of adrenal insufficiency.

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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 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 of immunomodulating agent
- 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
- Antacid therapy daily as gastric ulcer prevention while on steroids
- Review proper administration of steroids
- Take with food
- Clinical judgment to initiate prophylactic antibiotic or antifungal coverage
- Avoid alcohol/acetaminophen or other hepatotoxins
- Monitor other medications during steroid taper

RED FLAGS:
- Symptoms of adrenal insufficiency
- Sick-day instructions, vaccinations, etc
Thyroiditis

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?

Type of Thyroid Abnormality

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

Secondary hypothyroidism
- TSH >5, <10 mIU/L with normal free T4, T3
- TSH >10 mIU/L with normal or low free T4 & T3
- Secondary hypothyroidism
- TSH low or <0.01 mIU/L with normal or high free T3 or T4
- Subclinical hypothyroidism
- TSH >5, <10 mIU/L with normal free T4, T3
- Subclinical hypothyroidism

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

- Inflammation of the thyroid gland

Nursing Assessment

**Look:**
- Does the patient appear unwell?
- Changes in weight since last visit
  - Appears 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 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 low or < 0.01 mIU/L with normal or high free T4 or T3**
- 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 patients (e.g., beta blockers for tachycardia/murmur and immunotherapy holds for patients who have acute thyroiditis表现 in hypothyroidism) when symptoms are mild/tolerable
- Consider collaborative management with endocrinologist especially if the patient is hypothyroid, particularly if a thyroid scan is needed
- History of thyroid disorders does not increase or decrease risk of incidence
- Assess medication compliance with oral thyroid replacement or suppression
- Educate patient that hypothyroidism is generally not reversible

**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*
Care Step Pathway - Type 1 Diabetes Mellitus

Type 1 Diabetes Mellitus

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)

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

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
- Immunotherapy may be continued until blood glucose is regulated

Management

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

Fasting Glucose Value:

- Grade 5 (Potentially Life-Threatening) >500 mg/dL
- Grade 4 (Potentially Life-Threatening) 250–500 mg/dL
- Grade 3 (Severe) 160 – 250 mg/dL
- Grade 2 (Moderate) >160 mg/dL

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

DM = diabetes mellitus; ULN = upper limit of normal

DM = diabetes mellitus; ULN = upper limit of normal

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Risk of pneumonitis is greater in patients receiving combination immunotherapy regimens.

**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 steroid requirements to manage pneumonitis are high (1–4mg/kg/day) and patient will be on corticosteroid therapy for at least 1 month.
- Identify high-risk individuals (e.g., asthma, COPD) and those with cardiopulmonary symptoms prior to initiating immunotherapy. Establish a thorough baseline.

**Nursing Implementation:**

- Identify barriers to adherence.
- Assess patient & family understanding of recommendations and rationale ordered by provider.
- Anticipate that bronchoscopy may be ordered by provider if infection is excluded.
- Identify barriers to adherence, specifically compliance with medication, physical activity.
- Anticipate the use of empiric antibiotics until infection is excluded.
- Assess patient & family understanding of toxicity and rationale for treatment discontinuation.
- Anticipatory guidance on proper administration of medications (e.g., mycophenolate, cyclophosphamide).
- Additional supportive care medications may also be initiated.
- If symptoms do not improve within 48–72 hours, corticosteroid dose will be escalated. IV corticosteroids may be considered then slow taper over at least 1 month.
- Anticipate treatment with:
  - pembrolizumab, nivolumab.
- Review symptoms to watch for with patient and family, and remember to continue to monitor via radiology testing (q 2–4 weeks, as needed).
- Discontinue immunotherapy for Grade 3/4 events (resume when Grade 0/1).
- Discontinue immunotherapy for Grade 2 (Moderate) events (resume when Grade 0/1).
- Immunotherapy to be withheld for Grade 2.
- Immunotherapy to be continued for Grade 1 (Mild).
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 steroid requirements to manage pneumonitis are high (1–4mg/kg/day) and patient will be on corticosteroid therapy for at least 1 month
- Educate patients that new pulmonary symptoms should be reported immediately
- Identify high-risk individuals (e.g., asthma, COPD) and those with cardiopulmonary symptoms prior to initiating immunotherapy. Establish a thorough baseline

**Nursing Implementation:**
- Assess patient & family understanding of recommendations and rationale
- Anticipate that bronchoscopy may be ordered by provider or anticipated guidance on proper
- Consider mycophenolate, cyclophosphamide
- Anticipate the use of additional immunosuppressive agents if symptoms do not improve in 48–72 hours
- If symptoms do not improve within 48–72 hours, corticosteroid dose will be increased to 4mg/kg/day or equivalent) until symptoms improve to baseline, and then slow taper over at least 1 month
- Discontinue immunotherapy for Grade 3/4 events (ipilimumab, nivolumab, pembrolizumab)
- Discontinue immunotherapy for Grade 5 events (Death)
- Immunotherapy to be withheld for Grade 2, 3 events
- Continue to monitor via radiology testing (q 2–4weeks, as needed)
- Recurrent (pembrolizumab, nivolumab) or persistent Grade 2 events (ipilimumab, nivolumab) or recurrent (pembrolizumab, nivolumab) or persistent Grade 2 events (ipilimumab, nivolumab)
- No known interventions

**Prevention**
- Assess previous anxieties (resilience or cognition) or be proactive about discussing and addressing any need to assist in identifying a decrease at any onset.
- Every effort is made to maintain or improve physical function and quality of life.
- Assess for other side effects such as injection, pulmonary embolism, progressive lung metastasis, or lung disease.

**Management**
Arthralgias and Arthritis

### Grading Toxicity

#### Grade 0 (Mild)
- Low-dose corticosteroids (0.5 – 1 mg prednisone equivalent per day)
- Celecoxib
- Hydroxychloroquine

#### Grade 1 (Mild)
- Leflunomide
- Adalimumab
- Etanercept

#### Grade 2 (Moderate)
- Biologic DMARDs (bDMARDs)
- Low-dose corticosteroids
- Intravenous immunoglobulin
- Methotrexate

#### Grade 3 (Severe)
- TNF inhibitors
- Intraarticular steroids
- Opioids
- Non-biologic agents
- Anticoagulants

#### Grade 4 (Potentially Life Threatening)
- Pembrolizumab or nivolumab
- Other immunotherapies

#### Grade 5 (Death)
- No known interventions

### Nursing Assessment

#### Arthralgia

- Recognize:
  - Pain (new or worsening)
  - Associated symptom(s)
  - Fatigue (new or worsening)
  - Other symptoms
- Listen:
  - Does the patient appear uncomfortable?
  - Are symptoms limiting self-care ADL?
- Look:
  - Does the patient appear well-nourished?
  - Is their gait affected?
  - Does the patient have trouble getting up and down?

#### Arthritis

- Severe pain associated with signs of inflammation:
  - Erythema, or joint swelling
  - Moderate pain associated with inflammatory ADL
  - Mild pain with inflammation
- Does the patient appear unwell?
- Is there a history of prior orthopedic injury, DJD, OA, RA?
- Does the patient appear uncomfortable?
- Are symptoms limiting self-care ADL?
- Are symptoms increasing the patient’s risk for a fall? Other safety issues?
- Have symptoms worsened?
- Has the patient been referred?
- Is the patient having trouble getting up and down?
- Do the patient’s joints seem to be inflamed?
Management

**Arthralgias and Arthritis**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>OA (Osteoarthritis)</td>
<td>Pain in joints due to wear and tear of cartilage</td>
</tr>
<tr>
<td>RA (Rheumatoid Arthritis)</td>
<td>Inflammation of joints with destruction of cartilage</td>
</tr>
<tr>
<td>PsA (Psoriatic Arthritis)</td>
<td>Arthritis associated with psoriasis</td>
</tr>
</tbody>
</table>

**Symptoms of Arthritis**

- Joint pain
- Joint stiffness
- Limited motion
- Swelling
- Redness

**Diagnosis**

- Physical examination
- Laboratory tests: CBC, ESR, CRP, RF, ANA

**Prevention**

- Regular exercise
- Weight management
- Healthy diet

**Management**

1. **Nursing Implementation**
   - **Sulfasalazine** is associated with rash; do not use in patients with a history of rash.
   - **Duloxetine** is associated with nausea;告知患者可能出现的副作用。

2. **Assess patient & family understanding of toxicity**
   - **Potential for colonic perforation** within 6 weeks.

3. **Identify barriers to adherence**
   - **Rituximab** and **tocilizumab** are anti-IL-6 receptor blocking agents.

4. **Anticipate pre-visit assessment**
   - **CBC, ESR, CRP, BUN/CR, aminotransferases, ANA, RF**

5. **Anticipate referral to rheumatology**
   - For collaborative management and consideration of biologic agents.

6. **Anticipate continued therapy**
   - For Grade 2 events persisting for more than 4 weeks.

**Grading Toxicity**

- **Grade 1 (Mild)**
  - Symptoms improve with NSAIDs, corticosteroids, and other adjunct therapies
- **Grade 2 (Moderate)**
  - Symptoms improve with modification of physical function and impact on QOL
- **Grade 3 (Severe)**
  - Symptoms worsen with NSAIDs, corticosteroids, and other adjunct therapies
- **Grade 4 (Severe or Life-Threatening)**
  - Symptoms worsen with NSAIDs, corticosteroids, and other adjunct therapies

**Overall Strategy**

- Early intervention to maintain or improve physical function and impact on QOL
- Symptom control through the treatment of inflammation and pain is often achieved

**Risk of fall due to mobility issues**

- Educate patients that arthralgias and arthritis are the most commonly reported rheumatic and musculoskeletal irAEs with checkpoint inhibitors.

**Symptoms**

- Fatigue (new or worsening)
- Malaise
- Loss of appetite
- Weight loss
- Anorexia
- Nausea
- Vomiting
- Diarrhea
- Constipation
- Dysuria

**Rationale for treatment**

- Assess patient & family understanding of toxicity
- Rationale for treatment discontinuation

**Anticipator guidance on proper administration**

- Low-dose corticosteroids (0.5 – 1mg/kg/day) to be used.
- Oral: ibuprofen, naproxen, celecoxib
- Topical: diclofenac (gel or cream)
- Intraarticular steroids to be used for significant symptomatic joint(s)
- TNF inhibitors

**Management**

- **Pembrolizumab or nivolumab** to be withheld for first- or second-degree adverse events.
- **Ipilimumab** to be discontinued for any Grade 3/4 event.
- **Grade 5 (Death)**
  - Is the patient having trouble getting up and down stairs?
  - Does the patient appear unwell?
  - Are their gait affected?

**Assessment**

- Is there a pre-existing autoimmune dysfunction?
- Is there a history of prior orthopedic injury, DJD, OA, RA?
- Are symptoms limiting ADL?
- Are symptoms increasing the patient's risk for injury or fall?
- Does the patient appear troubled or discomforted (feel)

**Prevention**

- No known interventions
RED FLAGS:

- Educate patients that symptoms that persist beyond treatment completion or discontinuation
- Acute phase reactants (ESR, CRP) may be increased temporarily following treatment
- Arthralgia-like symptoms can range from mild (managed well with NSAIDs and low dose corticosteroids) to severe and erosive (requiring multiple immunosuppressant medications)
- Educate patients that arthralgias and arthritis are the most commonly reported rheumatic and musculoskeletal issues with checkpoint inhibitors
- Identify higher-risk individuals and those with underlying autoimmune dysfunction

Nursing Implementations:

- Anticipate use of analgesia
- Anticipate referral to rheumatology for collaborative management and consideration of adjunct treatment
- Anticipate use of analgesia
- Anticipate pre-visit assessment: CBC, ESR, CRP, ADLs

ARThralgias and Arthritis

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DMARD = disease-modifying antirheumatic drug; ESR = erythrocyte sedimentation rate; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis; QOL = quality of life; RA = rheumatoid arthritis; DJD = degenerative joint disease; CRADLs = activities of daily living; AML = acute myeloid leukemia; ANA = antinuclear antibody; BUN = blood urea nitrogen; CBC = complete blood count; CR = creatinine; CRP = C-reactive protein; DLD = 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; DJD = degenerative joint disease; CRADLs = activities of daily living; AML = acute myeloid leukemia; ANA = antinuclear antibody; BUN = blood urea nitrogen; CBC = complete blood count; CR = creatinine; CRP = C-reactive protein; DLD = degenerative joint disease; CRADLs = activities of daily living; AML = acute myeloid leukemia; ANA = antinuclear antibody; 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Care Step Pathway – Neuropathy (motor or sensory nerve impairment or damage)

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?

Grading of Neuropathy:

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
- Other medical issues that may cause symptoms

Other medical issues that may cause symptoms
- Does the patient have diabetes mellitus?
- Are there neuropsychiatric signs and symptoms?
- Does the patient have depression or anxiety?
- Laboratory values
- Radiographic changes
- Electroencephalogram

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

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
- Neurontin to be withheld for Grade 2 event persisting ≥ 12 weeks, or until to reduce steroid dose to ≤ 10 mg prednisone or equivalent per day

- Potential systemic therapy recommendations
- 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
- Monitoring of neuropathic pain
- Neuromuscular evaluations
- Pain management

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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?

Grading of Neuropathy:

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
- 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 \( \geq 6 \) weeks or inability to reduce steroid dose to \( \leq 7.5 \) mg prednisone or equivalent per day; pembrolizumab or nivolumab to be discontinued for Grade 3/4 events that recur, persist \( \geq 12 \) weeks, or inability to reduce steroid dose to \( \leq 10 \) 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

Grade 5 (Death)

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
- Compare baseline assessment; grade & document neuropathy and etiology (diabetic, medication, vascular, chemotherapy)
- Monitor for signs and symptoms of Guillain–Barré syndrome
- Monitor for signs and symptoms of myasthenia gravis

RED FLAGS:
- Guillain–Barré syndrome
- Myasthenia gravis
- Steroid taper instructions/calendar as guide but not an absolute
- Tapers should consider patient’s current symptom profile
- Red flags include consideration of other conditions (e.g., conditions amenable to sulfamethoxazole/trimethoprim double dose IV/W/F; single dose IV/IV/F; single dose IV/IV/F; single dose IV/IV/F)
- Close follow-up in person or by phone, based on individual need & symptomatology
- RED FLAGS:
- Guillain–Barré syndrome
- Myasthenia gravis

ADLS = activities of daily living

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Acute Kidney Injury, Elevated Creatinine

**Grading Toxicity**

- Creatinine >3×ULN or > 4.0 mg/dL; hospitalization indicated
- Creatinine 2–3×ULN
- Creatinine 1.5–2×ULN
- Creatinine level ≤ 0.3 mg/dL

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

**Incident:** Hospitalization indicated

**Nursing Assessment**

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

- Does the patient appear uncomplacent?
- Does the patient appear uncomfortable?
- Does the patient look ill?
- How much fluid is the patient taking in? (Frequency)
- Adequate hydration (casts)
- Altered mental status
- Malaise?
- Fever?
- Nausea?
- Urinalysis abnormalities (casts)
- Hypertension
- edema
- Nausea?
- Other symptoms concerning for: fever
- Abdominal pain
- Pyelonephritis?
- Urinary tract infection?
- Worsening CHF?
- Presence of current or prior immune-mediated inflammation of the kidneys
- Laboratory abnormalities (elevated creatinine, urinalysis abnormalities, casts)
- Recency of current or prior immune-mediated inflammation of the kidneys
- Current or recent use of nephrotoxic medications
- Are associated symptoms present?
- How much fluid is the patient taking in?
- The patient look ill?
- Hypertension
- Malaise?
- Nausea?
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- Other symptoms concerning for: fever
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- The patient look ill?
- Hypertension
- Malaise?
- Nausea?
- Nausea?
- Other symptoms concerning for: fever
- Abdominal pain
- Pyelonephritis?
- Urinary tract infection?
- Worsening CHF?
- Presence of current or prior immune-mediated inflammation of the kidneys
- Laboratory abnormalities (elevated creatinine, urinalysis abnormalities, casts)
- Recency of current or prior immune-mediated inflammation of the kidneys
- Current or recent use of nephrotoxic medications
- Are associated symptoms present?
- How much fluid is the patient taking in?
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- Current or recent use of nephrotoxic medications
- Are associated symptoms present?
- How much fluid is the patient taking in?
Nephritis Page 2 of 3

**Management**

- Early intervention to maintain or improve physical function and quality of life (QOL).
- Evaluation for progression kidney/immune-mediated metastases that may be contributing to kidney dysfunction
- Ensure adequate hydration daily
- Evaluate potential nephrotoxic medications
- Assess for other etiologies such as infection

**Criteria**

- Mild elevation in creatinine (Grade 1)
  - Creatinine level ≤0.3 mg/dL; hospitalization indicated
  - Grade 1 (Mild) nephritis

- Moderate elevation in creatinine (Grade 2)
  - Creatinine level >0.3 mg/dL; hospitalization indicated
  - Grade 2 (Severe) nephritis

- Severe elevation in creatinine (Grade 3)
  - Creatinine level ≥0.3 mg/dL; hospitalization indicated
  - Grade 3 (Severe)

- Potentially life-threatening (Grade 4)
  - Creatinine level ≥2 mg/dL; hospitalization indicated
  - Grade 4 (Potentially Life-Threatening)

**Risk Factors**

- Idiopathic disorders
- Acute interstitial nephritis seen from PD-1 inhibitors
- Lupus-like nephritis
- Granulomatous acute interstitial nephritis

**RED FLAGS:**

- New or worsening urinary symptoms
- Acute onset of kidney dysfunction
- Progressive kidney/adrenal/pelvic metastases that may be contributing to kidney dysfunction

**Anticipations**

- Acute interstitial nephritis
- Lupus-like nephritis
- Granulomatous acute interstitial nephritis

**Immunosuppressives**

- Systemic corticosteroids (e.g., prednisone 0.5–1 mg/kg/day, in divided doses)
- Immunosuppressives (e.g., cyclophosphamide, mycophenolate mofetil, azathioprine)
- Biologicals (e.g., rituximab, infliximab)
- Monoclonal antibodies (e.g., pembrolizumab, nivolumab)

**Corticosteroids**

- Systemic corticosteroids (e.g., prednisone 0.5–1 mg/kg/day, in divided doses)
- Taper over at least 1 month

**Immunosuppressives**

- Immunosuppressives will be considered
- Increase in frequency of creatinine monitoring

**Anticipations**

- Anticipate the need for fluid management
- Anticipate the use of IV fluid to ensure adequate hydration
- Anticipate the use of additional supportive care medications

**Care Pathway**

1. **Identify Barriers to Adherence**
   - Anticipate barriers to adherence
   - Assess patient/family understanding of recommendations and provider education

2. **Care Plan**
   - Anticipate the need for ongoing monitoring
   - Anticipate the need for consultation by nephrology
   - Anticipate the need for medication adjustments

3. **Nursing Implementation**
   - Anticipate the need for close monitoring of creatinine
   - Anticipate the need for close monitoring of creatinine
   - Anticipate the need for close monitoring of creatinine

4. **Anticipations**
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In addition to acute interstitial nephritis seen from PD-1 inhibitors, there are case reports of lupus-like nephritis and granulomatous acute interstitial nephritis.

**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.
- Educate patients and family about the rationale for discontinuation of immunotherapy in patients who develop severe nephritis.
- Always report the steroid requirements to manage immune-mediated nephritis if high (up to 1–2 mg/kg/d) and patients will be on corticosteroid therapy for at least 1 month.
- Educate patients that new unexplained symptoms should be reported immediately.
- Monitor creatinine more frequently if levels appear to be rising and for Grade 1 toxicity.
- Check kidney function prior to each dose of immunotherapy. Ensure baseline creatinine has been obtained.
- Identify individuals with pre-existing renal dysfunction prior to initiating immunotherapy. Ensure baseline creatinine has been obtained.
- Consider discontinuation of immune checkpoint inhibitors for first occurrence of Grade 2 event.
- Pembrolizumab or nivolumab to be withheld for first occurrence of Grade 3–4 event.
- Ipilimumab to be withheld for any Grade 2 event (until Grade 0/1).
- Monitor creatinine more frequently if levels appear to be rising and for Grade 1 toxicity.
- Check kidney function prior to each dose of immunotherapy. Ensure baseline creatinine has been obtained.
- Identify individuals with pre-existing renal dysfunction prior to initiating immunotherapy. Ensure baseline creatinine has been obtained.
- Consider discontinuation of immune checkpoint inhibitors for first occurrence of Grade 2 event.
APPENDIX 2
### Management of other AEs associated with nivolumab/ipilimumab therapy.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Common symptoms</th>
<th>Common management/anticipatory guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute respiratory distress syndrome</td>
<td>Severe shortness of breath, dyspnea, or rapid breathing, hypotension, confusion, and extreme fatigue</td>
<td>* Serious condition requiring hospitalization/expert care, including supplemental oxygen, often mechanical ventilation, and fluid management</td>
</tr>
</tbody>
</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 |
| Cardiotoxicity: cardiomyopathy, myocarditis, heart failure | Dyspnea, edema, fatigue, chest pain, arrhythmias, abdominal pain or ascites     | * Monitor weight, changes in breathing, extremity edema, chest/back/arm/jaw pain, pressure  
  * ECG, Echo, stress test cardiology referral, 2 mg/kg prednisone, discontinue therapy |
| Constipation/ abdominal pain (associated with nivolumab) | Infrequent stools/difficulty stooling, abdominal pain                            | * Increase fluid, fiber; use caution with use of laxatives  
  * Consider appropriate testing to evaluate bowel obstruction  
  * Anticipate standard nivolumab 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 (Grade 2-3) moderate to severe symptoms: rule out infectious or other causes; consult neurologist, obtain brain MRI and lumbar puncture  
  * For ipilimumab: Anticipate standard ipilimumab dose holds/discontinuations*; administer corticosteroids at dose of 1-2 mg/kg/d prednisone equivalents (or 2-4 mg/kg if necessary)  
  * For nivolumab: Withhold nivolumab for new-onset moderate to severe neurologic symptoms; evaluate as described above; if other etiologies are ruled out, administer corticosteroids and permanently discontinue nivolumab for immune-mediated encephalitis |
### Management of other AEs associated with nivolumab/ipilimumab therapy.
(Continued)

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<th>Common management/anticipatory guidance</th>
</tr>
</thead>
</table>
| 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* |
| 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 | • May indicate hepatotoxicity; check LFTs/lipase/amylase; standard supportive care  
• Anticipate dose holds/discontinuations* |
| Ocular: conjunctivitis, blepharitis, episcleritis, iritis, ocular myositis, scleritis, uveitis (associated with ipilimumab) | Blurry vision, double vision, or other vision problems, eye pain or redness | • Encourage patient to report any eye symptoms immediately  
• Obtain ophthalmology referral  
• Anticipate standard dose ipilimumab holds/discontinuations* |
### Management of other AEs associated with nivolumab/ipilimumab therapy.

(Continued)

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</thead>
<tbody>
<tr>
<td>Pyrexia</td>
<td>Elevated body temperature</td>
<td>• Standard supportive care related to cytokine release</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Consider infectious workup for prolonged elevated temperature</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Anticipate standard dose holds/discontinuations*</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>Pain, muscle weakness, vomiting, confusion, tea-colored urine</td>
<td>• Anticipate dose holds/discontinuations*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Intravenous fluids and corticosteroids (check creatine kinase levels)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>Cough, runny nose, sore throat, nasal breathing</td>
<td>• Standard supportive care</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Any cough needs to be evaluated for possible infection vs pneumonitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Anticipate standard nivolumab treatment holds*</td>
</tr>
</tbody>
</table>

*Dose holds/discontinuations*

For nivolumab: Withhold 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.

For ipilimumab: Withhold for any Grade 2 (moderate) AE, and resume treatment when AE returns to Grade 0 or 1; permanently discontinue for any Grade 3-4 (life-threatening) AE, persistent Grade 2 AE lasting ≥6 weeks, or inability to reduce corticosteroid dose to 7.5 mg/d prednisone or equivalent.