AIM AT MELANOMA FOUNDATION | MELANOMA NURSING INITIATIVE

Nivolumab for Melanoma A Nursing Tool From the Melanoma Nursing Initiative (MNI)

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

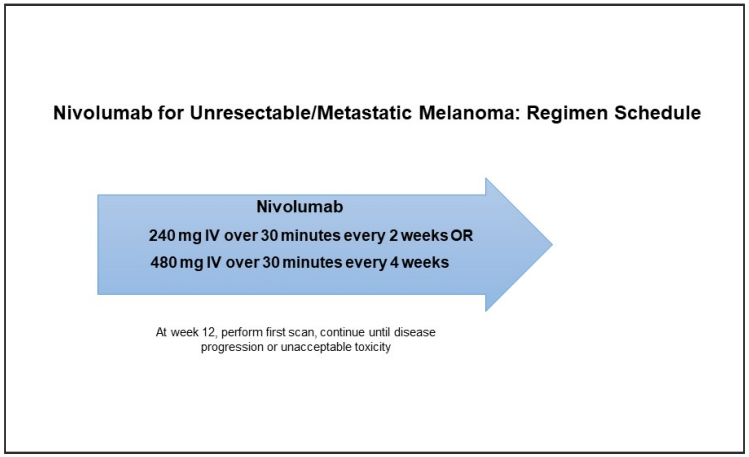
Nivolumab is indicated as monotherapy for the treatment of unresectable or metastatic (advanced) melanoma and for various other cancer types. Nivolumab is also indicated in combination with ipilimumab (Yervoy®) for the treatment of unresectable or metastatic melanoma (discussed in a separate nursing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

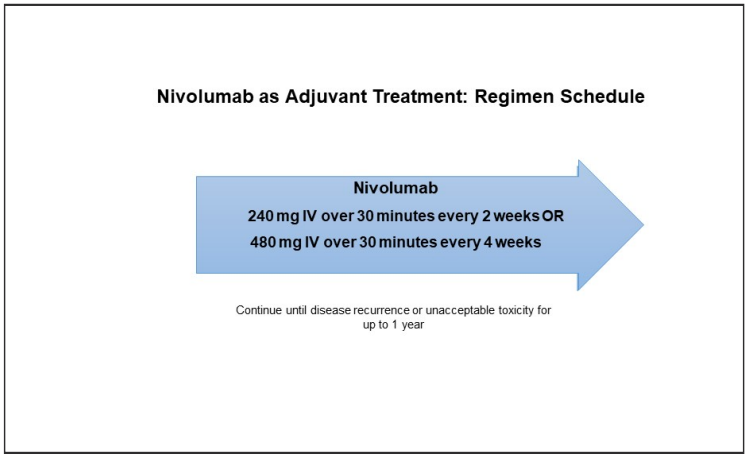
In December, 2017, the FDA approved nivolumab as an adjuvant treatment for patients with melanoma with involvement of lymph nodes (Stage III) or metastatic (Stage IV) disease who have undergone complete resection.

This document is part of an overall nursing toolkit intended to assist nurses in optimizing management of melanoma in patients receiving newer anti-melanoma therapies.

DRUG-DOSING/ADMINISTRATION

- For unresectable or metastatic melanoma, the recommended dose of nivolumab (Opdivo®) is 240 mg administered as an intravenous infusion over 30 minutes every 2 weeks or 480 mg every 4 weeks until disease progression or unacceptable toxicity
- For adjuvant treatment for patients with melanoma with involvement of lymph nodes (Stage III) or metastatic (Stage IV) disease who have undergone complete resection, the recommended dose of nivolumab (Opdivo®) is 240 mg administered as an intravenous infusion over 30 minutes every 2 weeks or 480 mg every 4 weeks until disease recurrence or unacceptable toxicity for up to 1 year





- Nivolumab is a clear to slightly opalescent, colorless to pale-yellow solution. Discard the vial if the solution is cloudy, discolored, or contains extraneous particulate matter (other than a few translucent-to-white, proteinaceous particles)
- To prepare the dose, withdraw the required volume of nivolumab and transfer it into an intravenous container. This should be diluted with either 0.9% Sodium Chloride injection, USP, or 5% Dextrose, USP to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL
- Mix the diluted solution by gentle inversion. Do not shake
- Do not coadminister nivolumab with other drugs through the same intravenous line
- Nivolumab is classified as an irritant and may be safely administered via a central or peripheral line. It is important to ensure IV access before administration. Nivolumab should be administered through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding in-line or add-on filter (pore size of 0.2 - 1.2 micrometers)

SIDE EFFECTS AND THEIR MANAGEMENT

Because nivolumab is an immunotherapy that works by enhancing the patient's immune system, most adverse reactions associated with nivolumab are related to overactivity of the patient's immune system (ie, immune-related adverse events [irAEs]). Various organ systems (often more than one) or tissues may be affected.

- Key to toxicity management:
  - » Proactive assessment for early signs/symptoms of toxicity
  - » Prompt intervention
  - » irAEs are typically managed with selective use of steroids
  - » In rare instances, toxicity may be steroid refractory, and additional immunosuppressive agents (mycophenolate mofetil, cyclophosphamide, etc) may be necessary
  - » Nivolumab will likely be held or discontinued depending on the severity and/or persistence of the irAE
  - » Referral to organ specialist should be considered, given that unique testing and management strategies may be required
- irAEs associated with nivolumab treatment can be categorized as those that are most common, less common but serious, and others that are easily overlooked
- Table 1 lists these irAEs and the corresponding Care Step Pathways in Appendix 1. Other adverse events associated with nivolumab are shown in Appendix 2

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

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

CLINICAL PEARLS

- PD-L1 status or elevated expression in not a prerequisite for nivolumab treatment of advanced melanoma
- It is important to monitor laboratory values at the start of treatment, periodically during treatment, and as indicated clinically
- Nivolumab-related irAEs may occur at any time, including after treatment completion or discontinuation
- Patients sometimes experience signs/symptoms that they think are due to “flu” or a cold, but that actually represent an irAE or an infusion reaction
- Endocrinopathies often present with vague symptoms (fatigue, headache, and/or depression) that can easily be overlooked or initially misdiagnosed. Hypervigilance and follow-up is important on the part of both nurses and patients
- IrAEs may become apparent upon tapering of corticosteroids, since they can be suppressed or masked by immunosuppressive therapy. Patients should be advised to be on the lookout for early signs of irAEs during the tapering period
- Endocrinopathies tend to occur somewhat more commonly with nivolumab or other PD-1 inhibitor therapies than with ipilimumab monotherapy
- Unlike other irAEs, endocrinopathies usually do not resolve and may require lifelong hormone replacement therapy
- Nurses should encourage patients to carry information about their nivolumab regimen with them at all times. This might be the nivolumab-specific wallet card, or at least emergency phone numbers and a list of side effects associated with the regimen. You may suggest that they paperclip the wallet and insurance cards together so information about their regimen will be shared whenever they show the insurance card
- Advise patients to take pictures of any skin lesions for documentation

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QUESTIONS & ANSWERS

Q. How long will patients stay on nivolumab?

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

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

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

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

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

Q. How do I counsel my patients about immunizations?

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

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PATIENT RESOURCES

Financial Assistance

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

Additional Information Resources

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

American Cancer Society Resource Section
http://www.cancer.org/cancer/melanoma-skin-cancer/treating/immunotherapy.html

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ADDITIONAL RESOURCES

- Boutros C, Tarhini A, Routier E, et al. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. *Nat Rev Clin Oncol*. 2016;13:473-486.
- Dadu R, Zobniw C, Diab A. Managing adverse events with immune checkpoint agents. *Cancer J*. 2016;22:121-129.
- Friedman CF, Proverbs-Singh TA, Postow MA. Treatment of the immune-related adverse effects of immune checkpoint inhibitors: a review. *JAMA Oncol*. 2016;2:1346-1353.
- Kumar V, Chaudhary N, Garg M, Floudas CS, Soni P, Chandra AB. Current diagnosis and management of immune related adverse events (irAEs) induced by immune checkpoint inhibitor therapy. *Front Pharmacol*. 2017;8:49. doi: 10.3389/fphar.2017.00049
- McGettigan S, Rubin KM. Managing adverse events with PD-1 inhibitor therapy of advanced melanoma: consensus statements from the faculty of the melanoma nursing initiative. *Clin J Oncol Nurs.* 2017;21(Suppl):42-51.
- Naidoo J, Page DB, Li BT, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint inhibitor antibodies. *Ann Oncol*. 2015;26:2375-2391.
- Opdivo® [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2018. Available at: http://packageinserts.bms.com/pi/pi_opdivo.pdf
- Opdivo patient alert card (wallet card) and other resources. http://www.opdivo.com/metastatic-melanoma/patient-caregiver-support/downloadable-resources
- Spain L, Diem S, Larkin J. Management of toxicities of immune checkpoint inhibitors. *Cancer Treat Rev*. 2016;44:51-60.
- Villadolid J, Amin A. Immune checkpoint inhibitors in clinical practice: update on management of immune-related toxicities. *Transl Lung Cancer Res*. 2015;4:560-577.
- Weber JS, Postow M, Lao CD, Schadendorf D. Management of adverse events following treatment with anti-programmed death-1 agents. *Oncologist*. 2016;21:1230-1240.

Click here for downloadable action plans to customize for your patients

APPENDIX 1

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? Is there a rash with or without pruritus?
- Are symptoms interfering with ADLs?
- With sleep?
- 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

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

PRURITUS

Definition: A disorder characterized by an intense itching sensation

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

Management

Overall Strategy

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

Intervention 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
- 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 SJN 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; SJN = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis

Care Step Pathway - Gastrointestinal Toxicity: Diarrhea and Colitis

Nursing Assessment

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

Listen:
- Quantity & quality of bowel movements (e.g., change in/ increased frequency over baseline): solid, soft, or liquid diarrhea; dark or bloody stools; or stools that float
- Fever
- Abdominal pain or cramping
- Increased fatigue
- Upset stomach, nausea, or vomiting
- Bloating/increased gas
- Decreased appetite or food aversions

Recognize:
- Serum chemistry/hematology abnormalities
- Infectious vs immune-related adverse event causation
- Peritoneal signs of bowel perforation (i.e., pain, tenderness, bloating)

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
- Dosage of steroids* to be increased:
  - Steroids* 1-2 mg/kg/day prednisone or equivalent: methylprednisolone (Solu-Medrol®)1 g IV (daily divided) doses
- Hospitalization
- GI consultation
- Assess for peritoneal signs, perforation (NPO & abdominal xray, surgical consult prn)
- Use caution with analgesics (opioids) and anti-diarrheal medications

Steroid* refractory: (if not responsive within 72 hours to high-dose IV steroid* infusion)
- Infliximab (Remicade®) 5 mg/kg infusion may be considered
- May require ≥1 infusion to manage symptoms (may re-administer at week 2 & week 6)
- Avoid with bowel perforation or sepsis
- PPD (tuberculin) testing not required in this setting
- 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

Grade 1 (Mild)
Asymptomatic or mild symptoms; intervention not indicated

Grade 2 (Moderate)
Moderate pain; not interfering with oral intake; modified diet indicated

Grade 3 (Severe)
Severe pain; interfering with oral intake

Grade 4 (Potentially Life-Threatening)
Life-threatening consequences; urgent intervention indicated

Grade 5 (Death)

Xerostomia (dry mouth)

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

Grade 1 (Mild)
Symptomatic (e.g., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 mL/min

Grade 2 (Moderate)
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

Grade 3 (Severe)
Inability to adequately aliment orally; tube feeding or total parenteral nutrition indicated; unstimulated saliva <0.1 mL/min

Grade 4 (Potentially Life-Threatening)
Life-threatening consequences; urgent intervention indicated

Grade 5 (Death)

Management (Including anticipatory guidance)

Overall Strategy

- Assess for other etiology of mucositis or dry mouth: candidiasis; ask patient about new medications (particularly antihistamines), herbals, supplements, alternative/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 Grade 2 events persisting ≥6 (ipilimumab) or ≥12 weeks (pembrolizumab, nivolumab)
- Assess for Sicca syndrome, Sjögren's syndrome
- Encourage vigilant oral hygiene

<u>Xerostomia:</u>

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

<u>Mucositis:</u>

- 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

Grades 3-4 (Severe or Life-Threatening)

- 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, pembrolizumab, nivolumab) or any recurrent Grade 3 event (pembrolizumab, nivolumab)
- Anticipate hospitalization if unable to tolerate oral solids or liquids
- Unclear role of systemic corticosteroids
- Anticipate need for supplemental nutrition
  - Enteral
  - Parenteral
- Anticipatory guidance regarding use of pharmacologic agents
  - Analgesics
    - Systemic opioids may be indicated
- Oral care
- Assess patient & family understanding of toxicity and rationale for interventions as well as treatment discontinuation
  - Identify barriers to adherence

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

Nursing Assessment

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

Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)	Grade 5 (Death)
AST/ALT: >ULN – 3.0× ULN	AST/ALT: >3.0× – 5.0× ULN	AST/ALT: >5.0× – 20.0× ULN	AST/ALT: >20× ULN	
Bilirubin: >ULN – 1.5× ULN	Bilirubin: >1.5× – 3.0× ULN	Bilirubin: >3.0× ULN	Bilirubin: >10× ULN	

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 <u>are not</u> recommended due to potential hepatotoxic effects

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)
- 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
- Consider starting steroids* 0.5 mg – 1 mg/kg/day prednisone or equivalent daily (IV methylprednisolone 125 mg total daily dose) + an anti-acid
- Consider hospital admission for IV steroids*
- If LFT normalized and symptoms resolved, steroids* to be tapered over ≥ 4 weeks when function recovers
- Once patient returns to baseline or Grade 0-1, consider resuming treatment

Grade 3 (Severe)

- Steroids* to be initiated at 2 mg/kg/day prednisone or equivalent daily oral
- 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
- Admission for IV steroids*
- R/O hepatitis infection (acute infection or reactivation)
- Daily LFTs
- If sustained elevation is significant and/or refractory to steroids* potential for ADDING to steroid regimen immunosuppressive agent:
  - CellCept® (mycophenolate mofetil) 500 mg - 1000 mg po q 12 hours OR
  - Antithymocyte globulin infusion
- Hepatology/gastroenterology consult
- Consider liver biopsy
- If LFTs stable/declining daily for 5 consecutive days: decrease LFT checks to q 3 days, then weekly
- If LFT normalized and symptoms resolved, steroids* to be tapered over ≥4 weeks

Grade 4 (Life-Threatening)

- Immunotherapy to be discontinued
- Hospital admission
- Steroids* to be initiated at 2 mg/kg/day prednisone or equivalent daily intravenous
- R/O hepatitis infection
- Daily LFTs
- If sustained elevation and refractory to steroids* potential for ADDING to steroid regimen:
  - CellCept® (mycophenolate mofetil) 500 mg - 1000 mg po or IV q 12 hours OR
  - Antithymocyte globulin infusion
- Hepatology/gastroenterology consult
- Consider liver biopsy
- If LFTs stable/declining daily for 5 consecutive days: decrease LFT checks to q 3 days, then weekly
- If LFTs normalized and symptoms resolved, steroids* to be tapered slowly over ≥4 weeks

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 hepatoxins

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

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

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)

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)

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)

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

- 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:

- **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

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

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

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

TSH low or <0.01 mIU/L with high free T4 or T3
Hyperthyroidism

Management

TSH low or <0.01 mIU/L with normal or high 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

Care Step Pathway - Type 1 Diabetes Mellitus (immune destruction of beta cells in pancreas)

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)

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

Grade 2 (Moderate)
Fasting glucose value >160 – 250 mg/dL

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

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

Grade 5 (Death)

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

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

Hypoxia

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

Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)	Grade 5 (Death)
	Decreased oxygen saturation with exercise (e.g., pulse ox <88%); intermittent supplemental oxygen	Decreased oxygen saturation at rest (e.g., pulse ox <88%)	Life-threatening airway compromise; urgent intervention indicated (tracheostomy, intubation)	

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.

Prevention

- No known interventions

Grade 1 (Mild)

- Anticipate immunotherapy to continue
- Continue to monitor via radiology testing (q 2–4 weeks, as needed)
- Review symptoms to watch for with patient and family, and remember to assess at every subsequent visit

Grade 2 (Moderate)

- Immunotherapy to be withheld for Grade 2 events (resume when Grade 0/1)
- Immunotherapy to be discontinued for recurrent (pembrolizumab, nivolumab) or persistent Grade 2 events (ipilimumab, pembrolizumab, nivolumab)
- Anticipate treatment with:
  - 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
  - If symptoms do not improve within 48–72 hours, corticosteroid dose will be escalated. IV corticosteroids may be considered
  - Additional supportive care medications may also be initiated
- Anticipatory guidance on proper administration
- Anticipate the use of empiric antibiotics until infection is excluded
- Anticipate that bronchoscopy may be ordered by provider
- Assess patient & family understanding of recommendations and rationale
- Identify barriers to adherence

Grades 3–4 (Severe or Life-Threatening)

- Discontinue immunotherapy for Grade 3/4 events
- Patient will likely need to be admitted to the hospital for further management and supportive care
- Anticipate the use of high-dose IV corticosteroids (e.g., methylprednisolone 2–4 mg/kg/day or equivalent)
- Once symptoms have resolved to baseline or Grade 1, convert to equivalent oral corticosteroid dose and then taper slowly over at least 1 month
- Anticipate the use of empiric antibiotics until infection is excluded
- Anticipate the use of additional immunosuppressive agents if symptoms do not improve in 48–72 hours (e.g., infliximab, mycophenolate, cyclophosphamide)
- Assess patient & family understanding of toxicity and rationale for treatment discontinuation
- Identify barriers to adherence, specifically compliance with medication, physical activity

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

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

Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)	Grade 5 (Death)
Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL		

Arthritis

Definition: A disorder characterized by inflammation involving a joint

Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)	Grade 5 (Death)
Mild pain with inflammation, erythema, or joint swelling	Moderate pain associated with signs of inflammation, erythema, or joint swelling; limiting instrumental ADL	Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self-care ADL		

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, aquatic exercise, focused dance program
- 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

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

Grade 2 (Moderate)

- 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 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
- Anticipate 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

Grades 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
  - Persists ≥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
- Anticipate 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
- 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

Grading of Neuropathy:

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)

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

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.

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

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 nivolumab monotherapy.

Adverse event	Common symptoms	Common management/anticipatory guidance
Anorexia	Decreased appetite	• Monitor weight; query patient about appetite/eating habits; advise dietary modification if necessary (should improve with time) • Anticipate standard dose holds/discontinuations* • Consider referral to nutrition services for counseling on best food choices to avoid excessive weight loss
Constipation/ abdominal pain	Infrequent stools/ difficulty stooling, abdominal pain	• Increase fluid, fiber; use laxatives with caution • Consider appropriate testing to evaluate bowel obstruction • Anticipate standard dose holds/discontinuations* for Grade 3 and Grade 4 (constipation with manual evacuation indicated, severe abdominal pain, or life-threatening consequences)
Embryo-fetal toxicity	—	• Advise of risk to fetus and recommend use of effective contraception during treatment and for 3 months after ipilimumab and for 5 months after nivolumab is discontinued • Advise patient to tell HCP immediately if they or their partner suspect they are pregnant while taking therapy
Encephalitis	Headache, fever, tiredness, confusion, memory problems, sleepiness, hallucinations, seizures, stiff neck	• New-onset, moderate-to-severe symptoms: rule out infectious or other causes • Counsel neurologist, obtain brain MRI, and lumbar puncture • Anticipate standard dose-holds and discontinuations*
Fatigue	Feeling tired; lack of energy	• Query patients regarding energy level; evaluate possible contributory factors, including infection, disease progression, and hematological and metabolic abnormalities; standard supportive care • Anticipate standard dose holds/discontinuations* • Fatigue that interferes with ADLs is concerning and should be evaluated for underlying causes.
Headache	Head pain	• Need to rule out brain metastases, encephalitis, or hypophysitis; otherwise, standard supportive care (should improve with time) • Headache occurring in conjunction with fatigue could be indicative of hypophysitis • Anticipate standard dose holds/discontinuations*

Management of other AEs associated with nivolumab monotherapy.

(Continued)

Adverse event	Common symptoms	Common management/anticipatory guidance
Infusion reaction	Chills/shaking, back pain, itching, flushing, difficulty breathing, hypotension, fever	• Nivolumab and/or ipilimumab: For mild/moderate (Grade 1–2) reactions: interrupt or slow rate of infusion; monitor to recovery. • For severe/life-threatening (Grade 3–4) reactions: Discontinue nivolumab and/or ipilimumab; manage anaphylaxis via institutional protocol; monitor. Premedication with an antipyretic and antihistamine may be considered for future doses
Insomnia	Difficulty falling or staying asleep	• Counsel patients on good sleep habits; prescription medications can be used if needed (Should improve over time) • Anticipate standard dose holds/discontinuations*
Nausea/vomiting	Vomiting, queasiness, RUQ or LUQ pain	• Standard supportive care is usually adequate • May indicate hepatotoxicity; check LFTs/lipase/amylase • Anticipate standard dose holds/discontinuations*
Upper respiratory tract infection	Cough, runny nose, sore throat, nasal breathing	• Evaluate potential causes—a dry cough and shortness of breath would increase concern for pneumonitis • Standard supportive care • Anticipate standard treatment holds*

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