Care Step Pathway Tools for Immune-Related Adverse Event Assessment and Management

Appendix A. Care Step Pathway: Skin Toxicities

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 (dry skin)
  - » Changes in skin pigment or color
- Is there oral involvement of the rash?
- Does the rash involve the genital-vaginal region? The scalp?

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, eczema, wounds, prior radiation to region, 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 towards the center 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); having psychological effect and limiting instrumental ADLs; rash covering >30% BSA with or without mild symptoms	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)
Mild or localized; topical intervention indicated	Widespread and intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification [thick, leathery skin], oozing/crusts); limiting instrumental ADLs; oral intervention indicated	Widespread and constant; limiting self-care ADLs or sleep; systemic corticosteroid or immunosuppressive therapy indicated	

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Appendix A. Care Step Pathway: Skin Toxicities (cont.)

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
- Moderate potency topical corticosteroids may 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)
- Consider holding pembrolizumab or nivolumab and monitor for improvement weekly. If no improvement, begin treatment with prednisone 1 mg/kg tapering over 4 weeks
- Ipilimumab will be withheld for any Grade 2 event
- High-potency topical corticosteroids to be used
- Oral corticosteroids* (0.5 mg/kg–1.0 mg/kg) and oral antihistamines/oral anti-pruritics can be used (high-potency topical corticosteroids can be considered for rash alone)
- 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 or pembrolizumab to be withheld for any Grade 3 (severe) and discontinued for Grade 4 (life-threatening) skin conditions or confirmed SJS or TEN; Ipilimumab to be permanently discontinued for any Grade 3/4 event
- High-potency topical corticosteroids to be used; anticipate hospitalization and initiation of IV corticosteroids* (0.1-1 mg/kg/day)
- Urgent 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.
- For Grade 3/4 pruritus
  - » Corticosteroid* dose 0.5-1.0 mg/kg/day
  - » Consider GABA agonist, aprepitant, or omalizumab
- Assess patient & family understanding of toxicity and rationale for treatment discontinuation
  - » Identify barriers to adherence, specifically adherence with steroids when transitioned to oral corticosteroids

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Appendix A. Care Step Pathway: Skin Toxicities (cont.)

*Administering Corticosteroids

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

- Taper should consider patient's current symptom profile
- Close follow-up in person or by phone, based on individual need and symptomatology
- Steroids cause indigestion; provide antacid therapy daily as gastric ulcer prevention while on steroids (e.g., proton pump inhibitor or H2 blocker if prednisone dosage is >20 mg/day)
- Review steroid medication side effects: mood changes (angry, reactive, hyperaware, euphoric, manic), increased appetite, interrupted sleep, oral thrush, fluid retention
- Be alert to recurring symptoms as steroids taper down and 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
- If extended steroid use, risk for osteoporosis; initiate calcium and vitamin D supplements

RED FLAGS

- Extensive rash (>50% BSA), or rapidly progressive
- Anal, genitourinary, vaginal, or any mucous membrane involvement
- Concern for suprainfection

ADLs = activities of daily living; BSA = body surface area; po = by mouth; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis. Copyright © 2019 IO Essentials.

Appendix B. Care Step Pathway: Gastrointestinal Toxicity (diarrhea and colitis)

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 (e.g., pain, tenderness, bloating)

Grading Toxicity

DIARRHEA (increased frequency; loose, large volume, or liquidy stools)

Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)	Grade 5 (Death)
• Increase of <4 stools/day over baseline • Mild increase in ostomy output compared with baseline	• Increase of 4–6 stools/day over baseline • Moderate increase of output in ostomy compared with baseline • Limiting instrumental ADLs	• Increase of ≥7 stools/day over baseline; incontinence • Hospitalization indicated • Severe increase in ostomy output compared with baseline • Limiting self-care ADLs	• Life-threatening (e.g., perforation, bleeding, ischemic necrosis, toxic megacolon) • Urgent intervention required	

COLITIS (inflammation of the intestinal lining)

Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)	Grade 5 (Death)
Asymptomatic; clinical or diagnostic observation only; intervention not indicated	Abdominal pain; blood or mucus in stool	Severe abdominal pain; peritoneal signs; medical intervention indicated	Life-threatening (e.g., hemodynamic collapse); urgent intervention indicated	

☞ *Table continued on the following page*

Appendix B. Care Step Pathway: Gastrointestinal Toxicity (diarrhea and colitis; cont.)

Management

Overall Strategy
- Rule out infectious, non-infectious, disease-related etiologies
- Assess patient & family understanding of recommendations and rationale
- Identify barriers to adherence

Grade 1 (Mild)
- May continue immunotherapy
- Consider loperamide

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

Grade 2 (Moderate)
- Send stool sample for *C. difficile* testing, culture, and ova and parasite
- Depending on institutional availability, consider fecal lactoferrin/calprotectin
- Consider gastroenterology consult (for flex sig/colonoscopy/endoscopy)
- Consider abdominal/pelvic CT (w/ contrast)
- Immunotherapy to be withheld until Grade ≤1 or patient's baseline (ipilimumab, pembrolizumab, nivolumab)
- Consider anti-diarrheals: Imodium® (loperamide) or Lomotil® (diphenoxylate/atropine)
- If upper or lower GI symptoms persist >5 days
  - » Oral steroids* to be started (prednisone 1 mg/kg/day or equivalent)
  - » After control of symptoms, a ≥4-week steroid* taper will be initiated
  - » If no response to corticosteroids* in 3 days, treat as steroid* refractory (see specific recommendations under Grades 3/4)
- 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
- Assure adequate hydration
- 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 reimaging
- 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 agents; consider resuming when toxicity resolves to ≤ Grade 1
  - » Grade 3: Ipilimumab to be discontinued as a single agent and nivolumab discontinued when given with ipilimumab
  - » Grade 3 (Recurrent): Permanently discontinue pembrolizumab or nivolumab
  - » Grade 4: Ipilimumab and/or PD-1 inhibitor to be permanently discontinued
- Dose of steroids* to be increased (from oral to IV):
  - » Steroids* 2 mg/kg/day prednisone or equivalent
- Hospitalization
- GI consultation
- Assess for peritoneal signs, perforation (npo & abdominal x-ray, surgical consult prn)
- Use caution with analgesics (opioids) and anti-diarrheal medications
- Steroid* taper to include IV to oral transition

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 infliximab 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
- Delaying infliximab infusion may have life-threatening consequences
- If infliximab not effective, consider vedolizumab 300 mg

Diet modification:
- Very strict with acute symptoms: clear liquids; very bland, low fiber and low residue (BRAT diet)
- May require complete gut rest
- Advance diet slowly as steroids* reduced to low doses
- Steroids* to be tapered slowly over at least 4 weeks
- Supportive medications for symptomatic management:
  - » Consider loperamide: 2 capsules at the onset & 1 with each diarrhea stool thereafter, with a maximum of 6 per day
  - » Consider diphenoxylate/atropine 1-4 tablets per day
  - » Simethicone when necessary

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Appendix B. Care Step Pathway: Gastrointestinal Toxicity (diarrhea and colitis; cont.)

Implementation

- Compare baseline assessment: grade & document bowel frequency and stool consistency
- Early identification and evaluation of patient symptoms
- Grade symptom & determine level of care and interventions required
- Use anti-diarrheals with caution, since overuse in patients with colitis can lead to toxic megacolon and bowel perforation
- Early intervention with lab work and office visit if colitis symptoms are suspected
- Diarrhea and colitis may occur together or separately

*Administering Corticosteroids

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

- Taper should consider patient's current symptom profile
- Close follow-up in person or by phone, based on individual need and symptomatology
- Steroids cause indigestion; provide antacid therapy daily as gastric ulcer prevention while on steroids (e.g., proton pump inhibitor or H2 blocker if prednisone dosage is >20 mg/day)
- Review steroid medication side effects: mood changes (angry, reactive, hyperaware, euphoric, manic), increased appetite, interrupted sleep, oral thrush, fluid retention
- Be alert to recurring symptoms as steroids taper down and 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
- If extended steroid use, risk for osteoporosis; initiate calcium and vitamin D supplements

RED FLAGS

- Rapid change in gastrointestinal function, decreased appetite
- Bloating, nausea
- More frequent stools, consistency change from loose to liquid
- Persistent abdominal pain
- Fever

ADLs = activities of daily living; npo = nothing by mouth; PD-1 = programmed cell death protein-1; po = by mouth.
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Appendix C. Care Step Pathway: Thyroiditis (inflammation of the thyroid gland)

Assessment

Look:
- Appear unwell?
- Changes in weight since last visit?
  - » Appear heavier? Thinner?
- Changes in hair texture/thickness?
- Appear hot/cold?
- Look fatigued?
- Sweating?
- Hyperactive or lethargic?
- Difficulty breathing?
- Swollen neck?

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

Recognize:
- Other immune-related toxicity?
- Prior thyroid dysfunction?
- Prior history of radiation therapy?
- Signs of thyroid storm (fever, tachycardia, sweating, dehydration, cardiac decompensation, delirium/psychosis, liver failure, abdominal pain, nausea/vomiting, diarrhea)
- Signs of airway compression
- Clinical presentation: Occasionally thyroiditis with transient hyperthyroidism (low TSH and high free T4) may be followed by more long-standing hypothyroidism (high TSH and low free T4)
- Differential diagnosis—Primary hypothyroidism: High TSH with low free T4; secondary (central) hypothyroidism due to hypophysitis: both TSH and free T4 are low (see Implementation section for more detail about testing)

Grading Toxicity

HYPOTHYROIDISM

Definition: A disorder characterized by decreased production of thyroid hormones from the thyroid gland

Asymptomatic, subclinical hypothyroidism, mildly elevated TSH TSH 4 to <10 mIU/L, normal free T4	**Asymptomatic, subclinical hypothyroidism, moderately elevated TSH** TSH >10, normal free T4	**Symptomatic, primary clinical hypothyroidism** Elevated TSH, low free T4 in symptomatic patient*	**Severely symptomatic, primary clinical hypothyroidism (myxedema)** Elevated TSH, low free T4 in severely symptomatic patient*	**Life-threatening, primary clinical hypothyroidism (myxedema coma)**	**Death**

*For normal or low TSH with low free T4 in a symptomatic patient, see hypophysitis CSP (secondary [central] hypothyroidism)

HYPERTHYROIDISM

Definition: A disorder characterized by excessive levels of thyroid hormone in the body

Asymptomatic hyperthyroidism; clinical or diagnostic observation only *OR* **TSH low (or <0.01 mIU/L) with normal T4**	**Symptomatic hyperthyroidism; limiting instrumental ADLs** *OR* **TSH low (or <0.01 mIU/L) with high free T4**	**Severe symptomatic hyperthyroidism in addition to TSH low or <0.01 mIU/L with high free T4 or T3**	**Life-threatening symptomatic hyperthyroidism in addition to TSH low or <0.01 mIU/L with high free T4; urgent intervention indicated**	**Death**

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Appendix C. Care Step Pathway: Thyroiditis (inflammation of the thyroid gland; cont.)

Management

HYPOTHYROIDISM

Asymptomatic, subclinical hypothyroidism, mildly elevated TSH
- Continue pembrolizumab, nivolumab, or ipilimumab
- Repeat TFTs in 4–6 weeks

Asymptomatic, subclinical hypothyroidism, moderately elevated TSH
- Continue pembrolizumab, nivolumab, or ipilimumab
- May consider monitoring without intervention and repeating levels in 2–4 weeks if asymptomatic
- Consider thyroid replacement
  - » 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

Symptomatic, primary clinical hypothyroidism
- Continue pembrolizumab, nivolumab, or ipilimumab
- Consider co-management with endocrinologist
- Initiate thyroid replacement therapy
  - » Levothyroxine dosage 1.6 µg per weight (kg) or 75–100 µg daily
  - » Repeat TSH in 4–6 weeks and titrate dose to reference range TSH
- Monitor AM cortisol level to exclude concomitant adrenal insufficiency

Severe or life-threatening primary clinical hypothyroidism (myxedema)
- Continue pembrolizumab, nivolumab, or ipilimumab
- Obtain endocrine consultation and/or emergency in-patient care (as needed for mental status changes and/or if patient comatose)
- Labs: cell count, electrolytes, glucose, thyroid function, liver function tests, cortisol, blood gas, cardiac workup
- Care may include hemodynamic support, warming blankets, intravenous thyroid replacement, glucose supplementation, antibiotics if needed
- Post acute care, TSH will be monitored with dose titration; educate patients about how to take the medication properly and precipitating factors for myxedema coma

HYPERTHYROIDISM

Asymptomatic hyperthyroidism; clinical or diagnostic observation only
- Continue pembrolizumab, nivolumab, or ipilimumab
- Standard therapy for hyperthyroidism (methimazole treatment)

Symptomatic and severely symptomatic hyperthyroidism
- For symptomatic hyperthyroidism: continue pembrolizumab, nivolumab, or ipilimumab
- For severe symptomatic hyperthyroidism: hold pembrolizumab, nivolumab, or ipilimumab
- Consider collaborative management with endocrinologist
- 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 to determine if patient is truly hyperthyroid with Graves-like etiology
- Acute thyroiditis usually resolves or progresses to hypothyroidism; thus, can repeat TFTs in 4–6 weeks—If TRAb high, obtain a thyroid uptake scan & collaborate with endocrinologist
- Short period of 1 mg/kg prednisone* or equivalent may be helpful in acute thyroiditis
- Consider radioactive iodine therapy or methimazole treatment
- 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

Life-threatening symptomatic hyperthyroidism (thyroid storm)
- Discontinue nivolumab, pembrolizumab, or ipilimumab
- Hospitalization; inpatient, intensive care management
- Thyroid-suppressive therapy to be provided
- Anticipate cooling measures, fluid resuscitation, electrolyte replacement, nutritional support
- Antipyretics, management of tachyarrhythmia
- Ventilatory support if needed—agitation to be managed carefully to avoid respiratory depression

☞ *Table continued on the following page*

Appendix C. Care Step Pathway: Thyroiditis (inflammation of the thyroid gland; cont.)

*Administering Corticosteroids

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

- Taper should consider patient's current symptom profile
- Close follow-up in person or by phone, based on individual need and symptomatology
- Steroids cause indigestion; provide antacid therapy daily as gastric ulcer prevention while on steroids (e.g., proton pump inhibitor or H2 blocker if prednisone dosage is >20 mg/day)
- Review steroid medication side effects: mood changes (angry, reactive, hyperaware, euphoric, manic), increased appetite, interrupted sleep, oral thrush, fluid retention
- Be alert to recurring symptoms as steroids taper down and 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
- If extended steroid use, risk for osteoporosis; initiate calcium and vitamin D supplements

Implementation

- Ensure that patient undergoes thyroid function tests prior to first dose, every 12 weeks while on PD-1 therapy and q3 weeks with ipilimumab and periodically in follow-up
- Educate patient that hypothyroidism is generally not reversible
  - » Assess patient and family understanding of recommendations and rationale
  - » Discuss proper technique for taking thyroid supplementation medication (i.e., without food, separating from interacting medications)
- Assess medication adherence with oral thyroid replacement or suppression
- Explain that history of thyroid disorders does not increase or decrease risk of thyroiditis
- Consider reducing starting dose of thyroid hormone supplementation to avoid hyperthyroidism in sensitive patients (e.g., elderly patients, those with comorbidities)
- It is important to distinguish between primary and secondary (central) hypothyroidism, since the latter is managed as hypophysitis. ACTH, morning cortisol, FSH, LH, TSH, free T4, and DHEA-S should be tested as well as estradiol (women) and testosterone (men). An MRI of the pituitary should be considered if there is confirmed central thyroid/adrenal insufficiency.

RED FLAGS

- Swelling of the thyroid gland causing compromised airway
- Thyroid storm (severe end of thyrotoxicosis—mental status changes, extremely elevated heart rate, blood pressure, body temperature, compromised organ function)
- Myxedema (changes in behavior/mental status, extreme fatigue/cold intolerance, shortness of breath, swelling of hands or feet)

ACTH = adrenocorticotropic hormone; ADLs = activities of daily living; DHEA-S = dehydroepiandrosterone sulfate; FSH = follicle-stimulating hormone; LH = luteinizing hormone; MRI = magnetic resonance imaging; PD-1 = programmed cell death protein 1; po = by mouth; TFT = thyroid function test; TRAb = thyroid stimulating hormone receptor antibodies; TSH = thyroid stimulating hormone. Copyright © 2019 IO Essentials.

Appendix D. Care Step Pathway: Hepatotoxicity (immunotherapy-induced inflammation of liver tissue)

Assessment

Look:
- Does the patient appear fatigued or listless?
- Does the patient appear jaundiced?
- Does the patient have yellowing of eyes?
- Does the patient appear itchy?
- 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?
- Increased itching?
- 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 or ALT: >ULN–3.0 × ULN AST or ALT abnormal baseline: >1.5–3.0 × ULN Bilirubin: >ULN–1.5 × ULN	AST or ALT: >3.0–5.0 × ULN Bilirubin: >1.5–3.0 × ULN	AST or ALT: >5.0–20.0 × ULN Bilirubin: >3.0–10.0 × ULN	AST or ALT: >20 × ULN Bilirubin: >10 × ULN	

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Appendix D. Care Step Pathway: Hepatotoxicity (immunotherapy-induced inflammation of liver tissue; cont.)

Management of Transaminitis (without elevated bilirubin)

Management of Grade 2 or worse transaminitis with bilirubin >1.5x ULN: follow Grade 4 recommendations

Overall Strategy

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

Infliximab infusions are NOT recommended due to potential hepatotoxic effects

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* dosage 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 dosage)
- Consider hospital admission for IV steroids*
- If LFTs 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 1–2 mg/kg/day prednisone or equivalent daily oral
- Nivolumab to be permanently discontinued for Grade 3 events. Ipilimumab to be discontinued for any Grade 3 event, 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)
- LFTs every 1–2 days
- 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 LFTs normalized and symptoms resolved, steroids* to be tapered over ≥4 weeks

Grade 4 (Life-Threatening)

- Immunotherapy to be permanently 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

☞ *Table continued on the following page*

Appendix D. Care Step Pathway: Hepatotoxicity (immunotherapy-induced inflammation of liver tissue; cont.)

Implementation

- Check hepatitis labs in any patient with a history of hepatitis
- Institute early identification and evaluation of patient symptoms
- Institute early intervention with lab work and office visit if hepatotoxicity is suspected
- Grade LFTs and any other accompanying symptoms
- As noted in overall strategy, do not use infliximab because of hepatotoxic effects
- Assess patient and family understanding of recommendations and rationale
- Identify barriers to adherence

*Administering Corticosteroids

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

- Taper should consider patient's current symptom profile
- Close follow-up in person or by phone, based on individual need and symptomatology
- Steroids cause indigestion; provide antacid therapy daily as gastric ulcer prevention while on steroids (e.g., proton pump inhibitor or H2 blocker if prednisone dosage is >20 mg/day)
- Review steroid medication side effects: mood changes (angry, reactive, hyperaware, euphoric, manic), increased appetite, interrupted sleep, oral thrush, fluid retention
- Be alert to recurring symptoms as steroids taper down and 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
- If extended steroid use, risk for osteoporosis; initiate calcium and vitamin D supplements

RED FLAGS

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

ALT = alanine aminotransferase; AST = aspartate aminotransferase; GI = gastrointestinal; LFT = liver function test; po = by mouth; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; ULN = upper limit of normal.
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Appendix E. Care Step Pathway: Hypophysitis (inflammation of the pituitary gland)

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?
  - » Changes in libido?

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
- Hypotension
- DDX adrenal insufficiency: low cortisol and high ACTH
- DDX primary hypothyroidism: low free T4 and high TSH

Grading Toxicity

Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)	Grade 5 (Death)
Asymptomatic or mild symptoms; clinical or diagnostic observation only (headache, fatigue)	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADLs	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or existing hospitalization indicated; limiting self-care ADLs	Urgent intervention required (severe ataxia)	

Management

Overall Strategy
- Consider endocrinology consult
- Diagnostic workup should be initiated if not already done: Monitor levels of ACTH, AM cortisol, TSH, T4, and electrolytes
- Additional workup for low libido, mood changes, and fatigue may include LH, FSH, testosterone, and estradiol
- Ipilimumab to be withheld for any symptomatic hypophysitis and discontinued for symptomatic reactions persisting ≥6 weeks or for inability to reduce steroid dosage to ≤7.5 mg prednisone or equivalent per day
- Nivolumab to be withheld for Grade 2/3 hypophysitis and permanently 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
- May hold checkpoint inhibitors for any symptoms suspect for hypophysitis and restart after stabilized on hormone therapy
- Long-term supplementation of affected hormones is often required
  - » Secondary hypothyroidism requiring levothyroxine replacement
  - » Secondary hypoadrenalism requiring hydrocortisone replacement
    - Typical dosage: 20 mg qAM and 10 mg qPM
  - » Steroids should start several days prior to any thyroid replacement to prevent adrenal crisis
- 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)
- Medical alert bracelet is indicated

☞ *Table continued on the following page*

Appendix E. Care Step Pathway: Hypophysitis (inflammation of the pituitary gland; cont.)

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])
- Advise patients about medical alert bracelet, etc., stress doses of hydrocortisone or infection, etc.

*Administering Corticosteroids

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

- Taper should consider patient's current symptom profile
- Close follow-up in person or by phone, based on individual need and symptomatology
- Steroids cause indigestion; provide antacid therapy daily as gastric ulcer prevention while on steroids (e.g., proton pump inhibitor or H2 blocker if prednisone dosage is >20 mg/day)
- Review steroid medication side effects: mood changes (angry, reactive, hyperaware, euphoric, manic), increased appetite, interrupted sleep, oral thrush, fluid retention
- Be alert to recurring symptoms as steroids taper down and 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
- If extended steroid use, risk for osteoporosis; initiate calcium and vitamin D supplements

RED FLAGS

- Symptoms of adrenal insufficiency
- New onset of severe headache or vision changes

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; po = by mouth; TSH = thyroid stimulating hormone. Copyright © 2019 IO Essentials.

Appendix F. Care Step Pathway: Adrenal Insufficiency, primary (a disorder in which the adrenal cortex does not produce enough cortisol or aldosterone, which is caused directly by adrenal inflammation)

Assessment

Look:
Does the patient appear:
- Lethargic?
- Irritable?
- To have lost weight?
- Depressed?
- Weak?
- Bronze/dark colored (hyperpigmented)?
- Thinner?
- Sweaty?
- In pain (back, lower legs, abdomen, head)?
- Syncopal?
- Dry skin?
- Cold?
- Forgetful?

Listen:
- Fatigue
- Weakness
- Feeling cold all the time
- Loss of appetite
- Abdominal pain
- Nausea/vomiting
- Diarrhea
- Faint/dizzy when standing
- Mood change (irritable/depressed)
- Craving salty food
- Recurrent or severe headaches
- Irregular menstruation (women)
- Loss of libido
- Skin changes: dry, darkening
- Fever
- Persistent or worsening forgetfulness

Recognize:
- AM cortisol, ACTH stimulation test
- Primary vs secondary adrenal insufficiency (AI)
  - » Primary AI: A **low** morning cortisol (<5 mcg/dL) plus a **high** ACTH with or without abnormal electrolyte levels and symptoms (other criteria: 30–60-minute cortisol <18 mcg/dL after ACTH stimulation with above findings)
  - » Secondary AI: **low** morning cortisol plus **low or delayed** ACTH levels (on ACTH stimulation test)
  - » High plasma renin activity (primary) vs normal (secondary)
- Hyponatremia, hyperkalemia, hypoglycemia, hypercalcemia
- Orthostatic hypotension
- Imaging of adrenal and pituitary glands consistent with primary vs secondary adrenal insufficiency
- Fever, which may precipitate adrenal crisis
- Symptoms and laboratory findings of adrenal crisis

Grading Toxicity

PRIMARY ADRENAL INSUFFICIENCY

Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)	Grade 5 (Death)
Asymptomatic; clinical or diagnostic observations only	Moderate symptoms	Hospitalization indicated	Urgent intervention indicated	

☞ *Table continued on the following page*

Appendix F. Care Step Pathway: Adrenal Insufficiency, primary (a disorder in which the adrenal cortex does not produce enough cortisol or aldosterone, which is caused directly by adrenal inflammation; cont.)

Management

Grade 1 (Mild)
- Continue pembrolizumab, nivolumab, or ipilimumab
- Hydrocortisone (20 mg AM and 10 mg PM, then slowly titrate to lowest dose possible to normalize laboratory values) OR prednisone 5- to 10-mg starting dose*
- Fludrocortisone 0.1 mg every other day
- Advise a high sodium diet and adequate calcium/vitamin D intake
- Patient education regarding adrenal crisis and requirements for stress doses of corticosteroids

Grade 2 (Moderate)
- Withhold pembrolizumab, nivolumab, or ipilimumab
- Hydrocortisone (20 mg AM and 10 mg in PM, then slowly titrate to lowest dose possible according to symptoms) OR prednisone 5- to 10-mg starting dose*
- Fludrocortisone at 0.1 mg every other day; then titrate to symptoms
- Advise a high sodium diet and adequate calcium/vitamin D intake
- Patient education regarding adrenal crisis and requirements for stress doses of corticosteroids (if acutely ill, may need to double or triple dose for first 24–48 hours)
- Resume checkpoint inhibitors in patients who are no longer symptomatic (Grade 0 to 1)

Grades 3/4 (Severe or Life-Threatening)
- Withhold checkpoint inhibitors for Grade 3 and withhold or consider permanent discontinuation for Grade 4
- Patients require hospitalization and potentially intensive care under the guidance of an endocrinologist
- For Grade 3, double or triple oral corticosteroid doses should be initiated for 24–48 hours
- For Grade 4, high-dose steroids should be started immediately (hydrocortisone 100 mg IV immediately followed by hydrocortisone 200 mg/d as a continuous infusion for 24 h, reduced to hydrocortisone 100 mg/d the following day)
- If hemodynamically unstable, may require additional fluids (e.g., rapid infusion of 1000 mL isotonic saline [or more if needed within the first hour] or 5% glucose in isotonic saline, followed by continuous IV isotonic saline guided by individual patient needs)
- Tapering of stress doses of corticosteroids to more physiologic dosing under the guidance of the endocrinologist
- If not permanently discontinued, resume checkpoint inhibitors in patients who are no longer symptomatic (Grade 0 to 1)

☞ *Table continued on the following page*

Appendix F. Care Step Pathway: Adrenal Insufficiency, primary (a disorder in which the adrenal cortex does not produce enough cortisol or aldosterone, which is caused directly by adrenal inflammation; cont.)

Implementation

- CAUTION: Start corticosteroid* first before any other hormone replacement to avoid adrenal crisis
- Monitor clinical chemistries prior to each dose and check ACTH as indicated based on labs or symptoms
- Consider endocrinology referral
- Rule out other potential causes of primary adrenal insufficiency including infection (TB), adrenal metastases, amyloidosis, medications (antifungals), or inadequate tapering of corticosteroids
- Provide patient/caregiver education regarding:
  - » Understanding that the corticosteroids are for physiologic replacement and will be continued indefinitely
  - » Need for stress doses of corticosteroids for surgery, severe injury, or illness
  - » Importance of wearing a medical alert bracelet and carrying corticosteroids at all times in case of adrenal crisis (as well as knowledge of how to administer)

*Administering Corticosteroids

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

- Taper should consider patient's current symptom profile
- Close follow-up in person or by phone, based on individual need and symptomatology
- Steroids cause indigestion; provide antacid therapy daily as gastric ulcer prevention while on steroids (e.g., proton pump inhibitor or H2 blocker if prednisone dosage is >20 mg/day)
- Review steroid medication side effects: mood changes (angry, reactive, hyperaware, euphoric, manic), increased appetite, interrupted sleep, oral thrush, fluid retention
- Be alert to recurring symptoms as steroids taper down and 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
- If extended steroid use, risk for osteoporosis; initiate calcium and vitamin D supplements

RED FLAGS

Adrenal crisis:

- Sudden severe pain in the lower back, abdomen, and legs
- Severe weakness
- Severe vomiting and diarrhea
- Severe hypotension
- Severe dehydration
- Confusion, delirium
- Loss of consciousness

ACTH = adrenocorticotropic hormone; po = by mouth. Copyright © 2019 IO Essentials.

Appendix G. Care Step Pathway: Type 1 Diabetes Mellitus (immune destruction of beta cells in pancreas)

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?
- Confusion, altered level of consciousness with advanced cases

Recognize:
- Symptoms of diabetes
- Serum glucose levels
- Other immune-related toxicity (and any corticosteroids given)
- Infections

Grading Toxicity

Mild hyperglycemia
New-onset hyperglycemia glucose >ULN–200 mg/dL OR history of type 2 DM with low suspicion of DKA

Moderate or worse hyperglycemia (likely new-onset type 1 diabetes); no DKA
New-onset fasting glucose >200 mg/dL or random blood glucose >250 mg/dL OR history of type 2 DM with fasting/random glucose >250 mg/dL; DKA workup negative

Moderate or worse hyperglycemia (likely new-onset type 1 diabetes); DKA
New onset fasting glucose >200 mg/dL or random blood glucose >250 mg/dL OR history of type 2 DM with fasting/random glucose >250 mg/dL; DKA workup positive

Management

Overall Strategy
- Evaluate for symptoms of DKA in patients with new onset fasting glucose >200 mg/dL or random blood glucose >250 mg/dL OR history of type 2 DM with fasting/random glucose >250 mg/dL: excessive thirst, frequent urination, general weakness, vomiting, confusion, abdominal pain, dry skin, dry mouth, increased heart rate, and fruity odor on the breath
- If DKA is suspected, evaluate per institutional guidelines, including blood pH, basic metabolic panel, urine or serum ketones/anion gap positive. Consider C-peptide if urine or serum ketones/anion gap is positive.
- If type 1 DM is suspected, also consider anti-GAD, anti-islet cell antibodies
- High-dose corticosteroid* use for other immune-related adverse events may induce or exacerbate hyperglycemia; if corticosteroid-induced hyperglycemia is suspected, evaluate benefit: risk ratio of tapering corticosteroid for glucose control vs management of the immune-related adverse event

Mild hyperglycemia
- Continue pembrolizumab, nivolumab, or ipilimumab
- Monitor serial blood glucose at each dose
- Institute diet/lifestyle modification
- If necessary, provide antidiabetes medication per institutional protocol
- Consider endocrine consultation if patient is symptomatic/hyperglycemia cannot be controlled

Moderate or worse hyperglycemia (likely new-onset type 1 diabetes); No DKA
- Continue pembrolizumab, nivolumab, or ipilimumab
- Consider endocrinology management for type 1 DM
- Monitor serial blood glucose at each dose
- Institute diet/lifestyle modification
- Provide antidiabetes medication per institutional protocol

Moderate or worse hyperglycemia (likely new-onset type 1 diabetes); DKA
- Hold pembrolizumab, nivolumab, or ipilimumab
- Obtain endocrinology consultation
- Provide inpatient care
- Insulin to be provided as directed by inpatient team and/or endocrinologist
- DKA to be managed per institutional guidelines (e.g., intravenous fluids, potassium supplementation, intravenous insulin, hourly glucose, serum ketones, blood pH, and anion gap)
- Consider resuming immune checkpoint inhibitor therapy once DKA has been corrected and glucose level has been stabilized

☞ *Table continued on the following page*

Appendix G. Care Step Pathway: Type 1 Diabetes Mellitus (immune destruction of beta cells in pancreas; cont.)

Implementation

- For patients with new-onset type 1 diabetes, discuss that it will most likely be permanent
- Review signs and symptoms of hyper/hypoglycemia
- Follow patients closely with checks on blood glucose levels, signs of DKA (fruity breath, confusion, nausea, etc), and other symptoms (e.g., increased infections)
- Provide insulin education (or refer)
- Discuss possibility of other immune-related AEs, including others of endocrine origin
- Discuss dietary modification

*Administering Corticosteroids

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

- Taper should consider patient's current symptom profile
- Close follow-up in person or by phone, based on individual need and symptomatology
- Steroids cause indigestion; provide antacid therapy daily as gastric ulcer prevention while on steroids (e.g., proton pump inhibitor or H2 blocker if prednisone dosage is >20 mg/day)
- Review steroid medication side effects: mood changes (angry, reactive, hyperaware, euphoric, manic), increased appetite, interrupted sleep, oral thrush, fluid retention
- Be alert to recurring symptoms as steroids taper down and 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
- If extended steroid use, risk for osteoporosis; initiate calcium and vitamin D supplements

DKA = diabetic ketoacidosis; DM = diabetes mellitus; GAD = glutamic acid decarboxylase; po = by mouth; ULN = upper limit of normal. Copyright © 2019 IO Essentials.

Appendix H. Care Step Pathway: Pneumonitis (inflammation of lung alveoli)

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?
  - » Is it a dry cough or a productive 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 ambulation?
- Is there a pre-existing pulmonary autoimmune condition (e.g., sarcoidosis)?
- Does patient have lung metastases?
- History of radiation to the lung?
- 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; confined to one lobe of lung; 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)	

☞ *Table continued on the following page*

Appendix H. Care Step Pathway: Pneumonitis (inflammation of lung alveoli; cont.)

Management

Overall Strategy

- Assess for other etiologies such as infection (e.g., nasal swab for viral pathogens; sputum culture), pulmonary embolism, progressive lung metastases, pleural effusion, or lung disease
- Early intervention to maintain or improve physical function and impact on QOL
- Assess pulse oximetry (resting and on exertion) at baseline and at each visit to assist in identifying a decrease at early onset
- Consider chest CT or x-ray for assessment of efficacy of steroids/monitor for new lung metastases
- Assess patient and family understanding of recommendations and rationale
- Identify barriers to adherence, including adherence with medication, physical activity

Prevention

- Decrease or cease smoking; preventive vaccinations for flu and pneumonia

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 & family, and remember to assess at every subsequent visit
- Continue monitoring pulse oximetry (resting and with ambulation)
- Assess patient & family understanding of recommendations and rationale
- Identify barriers to adherence

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)
- Monitor pulse oximetry (resting and with ambulation) q 3–7 days
- 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 if no improvement in 72 hours, treat as Grade 3
  - » Additional supportive care medications may also be initiated
- Anticipatory guidance on proper administration of IV corticosteroids
- Anticipate the use of empiric antibiotics until infection is excluded
- Anticipate that bronchoscopy may be ordered by provider

Grades 3/4 (Severe or Life-Threatening)

- Permanently discontinue immunotherapy for Grade 3/4 events
- Obtain pulmonary and ID consults
- 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 1–4 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, IVIG)
- Assess patient & family understanding of rationale for treatment discontinuation
- Identify barriers to adherence, specifically compliance with medication, physical activity

☞ *Table continued on the following page*

Appendix H. Care Step Pathway: Pneumonitis (inflammation of lung alveoli; cont.)

*Administering Corticosteroids

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

- Taper should consider patient's current symptom profile
- Close follow-up in person or by phone, based on individual need and symptomatology
- Steroids cause indigestion; provide antacid therapy daily as gastric ulcer prevention while on steroids (e.g., proton pump inhibitor or H2 blocker if prednisone dosage is >20 mg/day)
- Review steroid medication side effects: mood changes (angry, reactive, hyperaware, euphoric, manic), increased appetite, interrupted sleep, oral thrush, fluid retention
- Be alert to recurring symptoms as steroids taper down and 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
- If extended steroid use, risk for osteoporosis; initiate calcium and vitamin D supplements

Implementation

- Identify high-risk individuals (e.g., asthma, COPD, prior thoracic radiation therapy) and those with cardiopulmonary symptoms prior to initiating immunotherapy. Establish a thorough baseline, including pulse oximetry (resting and with ambulation).
- Educate patients that new or worsening/changing pulmonary symptoms should be reported immediately
- Anticipate that the steroid requirements to manage pneumonitis are high (1–2 mg/kg/day) and patient will be on corticosteroid therapy for at least 1 month
- Educate patients & family about the rationale for discontinuation of immunotherapy in patients who do develop moderate or severe pneumonitis
- For severe/life-threatening pneumonitis, treat patient as immunocompromised, so ID workup to include nasal swab (viral), sputum, blood, and urine cultures

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

ADLs = activities of daily living; COPD = chronic obstructive pulmonary disease; IVIG = intravenous immunoglobulin; po = by mouth. Copyright © 2019 IO Essentials.

Appendix I. Care Step Pathway: Arthralgias and Arthritis

Assessment

Look:
- Does the patient appear uncomfortable?
- Does the patient appear unwell?
- Is 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 RA
  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		

☞ *Table continued on the following page*

Appendix I. Care Step Pathway: Arthralgias and Arthritis (cont.)

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

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 dosage 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
- Follow-up monitoring after diagnosis of arthritis/arthralgias (q 4–6 weeks after treatment initiation): CBC, ESR, CRP, BUN/Cr & aminotransferases, ANA, RF
- Intraarticular steroids to be used for significant symptomatic joint(s)
- Low-dose corticosteroids* (0.5 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 permanently discontinued if:
  - » Grade 3/4 event recurs
  - » Persists ≥12 weeks
- Ipilimumab to be permanently discontinued for any Grade 3/4 event
- High-dose steroids to be used (1 mg/kg) daily (rapid effect within days)
  - » Anticipatory guidance on proper administration
  - » Onset of action is rapid, typically within days
- If no improvement with corticosteroids in 2 weeks, consider infliximab or tocilizumab
- Anticipate referral to rheumatology for collaborative management and adjunct treatment
  - » Nonbiologic 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 (CD20 blocking)
      - ♦ Rituximab
  - » Agents NOT advised
    - 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

☞ *Table continued on the following page*

Appendix I. Care Step Pathway: Arthralgias and Arthritis (cont.)

*Administering Corticosteroids

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

- Taper should consider patient's current symptom profile
- Close follow-up in person or by phone, based on individual need and symptomatology
- Steroids cause indigestion; provide antacid therapy daily as gastric ulcer prevention while on steroids (e.g., proton pump inhibitor or H2 blocker if prednisone dosage is >20 mg/day)
- Review steroid medication side effects: mood changes (angry, reactive, hyperaware, euphoric, manic), increased appetite, interrupted sleep, oral thrush, fluid retention
- Be alert to recurring symptoms as steroids taper down and 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
- If extended steroid use, risk for osteoporosis; initiate calcium and vitamin D supplements

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; irAE = immune-related adverse event; JAK = Janus kinase; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis; po = by mouth; QOL = quality of life; RA = rheumatoid arthritis; RF = rheumatoid factor; TNF = tumor necrosis factor. Copyright © 2019 IO Essentials.

Appendix J. Care Step Pathway: Mucositis and Xerostomia

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)?
  - » Pain with swallowing/throat pain?
- Have symptoms worsened?

Recognize:
- Any history of dry mouth?
- Any history of radiation to the mouth?
- 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 ulceration or inflammation of the oral mucosa

Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)	Grade 5 (Death)
Asymptomatic or mild symptoms; intervention not indicated	Moderate pain or ulcer; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	

DRY MOUTH (XEROSTOMIA)

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

Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)	Grade 5 (Death)
Symptomatic (e.g., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 mL/min	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	Inability to adequately aliment orally; tube feeding or total parenteral nutrition indicated; unstimulated saliva <0.1 mL/min	Life-threatening consequences; urgent intervention indicated	

☞ *Table continued on the following page*

Appendix J. Care Step Pathway: Mucositis and Xerostomia (cont.)

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 weeks (ipilimumab) or ≥12 weeks (pembrolizumab, nivolumab)
- Assess for Sicca syndrome, Sjögren syndrome
- Encourage vigilant oral hygiene

Xerostomia:

- Advise moistening agents
  - » Saliva substitute
  - » Synthetic saliva
  - » Oral lubricants
  - » Saliva stimulants (XyliMelts®)
- Advise secretagogues
  - » Nonpharmacologic
    - Sugarless gum
    - Sugarless hard candies
    - Natural lemon
  - » Pharmacologic
    - Pilocarpine
    - Cevimeline HCl

Mucositis:

- Vigilant oral hygiene
  - » Increase frequency of brushing to q 4 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 nonacidic 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, prednisolone oral solution (24 mg/5 mL), hydrocortisone 2 mg/mL, 1–2 tsp swish/spit 2 × daily
  - » Monitor weight
  - » Monitor hydration status
- Nutrition referral if appropriate
- Assess patient & family understanding of toxicity and rationale for interventions as well as treatment hold
  - » Identify barriers to adherence
- Avoid morphine mouthwashes
- If persistent, consider biopsy or otolaryngology evaluation

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

☞ *Table continued on the following page*

Appendix J. Care Step Pathway: Mucositis and Xerostomia (cont.)

*Administering Corticosteroids

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

- Taper should consider patient's current symptom profile
- Close follow-up in person or by phone, based on individual need and symptomatology
- Steroids cause indigestion; provide antacid therapy daily as gastric ulcer prevention while on steroids (e.g., proton pump inhibitor or H2 blocker if prednisone dosage is >20 mg/day)
- Review steroid medication side effects: mood changes (angry, reactive, hyperaware, euphoric, manic), increased appetite, interrupted sleep, oral thrush, fluid retention
- Be alert to recurring symptoms as steroids taper down and 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
- If extended steroid use, risk for osteoporosis; initiate calcium and vitamin D supplements

po = by mouth. Copyright © 2019 IO Essentials.

Appendix K. Care Step Pathway: Neuropathy (motor or sensory nerve impairment or damage)

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
- Past history of toxicities with other therapies
- 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 Toxicity: ULN

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 instrumental ADLs

Peripheral Sensory:
- Moderate symptoms; limiting instrumental 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
- Screen for neuropathy causes: diabetes with HbA1C, vit B12, folates, TSH, and HIV
- Rule out infectious, noninfectious, disease-related etiologies (medications, metabolic/endocrine disorders, environmental exposures, vascular or autoimmune, trauma)
- High-dose steroids* (0.5–1 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* dosage 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 dosage to ≤10 mg prednisone or equivalent per day
- Guillain–Barré syndrome to be managed in the ICU setting, with particular attention to protection of the airway
- Neurology consult
  - » Consideration of electromyelography 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 symptom management (e.g., gabapentin, pregabalin, or duloxetine)

☞ *Table continued on the following page*

Appendix K. Care Step Pathway: Neuropathy (motor or sensory nerve impairment or damage; cont.)

Implementation

- Compare baseline assessment; grade and 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

*Administering Corticosteroids

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

- Taper should consider patient's current symptom profile
- Close follow-up in person or by phone, based on individual need and symptomatology
- Steroids cause indigestion; provide antacid therapy daily as gastric ulcer prevention while on steroids (e.g., proton pump inhibitor or H2 blocker if prednisone dosage is >20 mg/day)
- Review steroid medication side effects: mood changes (angry, reactive, hyperaware, euphoric, manic), increased appetite, interrupted sleep, oral thrush, fluid retention
- Be alert to recurring symptoms as steroids taper down and 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
- If extended steroid use, risk for osteoporosis; initiate calcium and vitamin D supplements

RED FLAGS

- Guillain–Barré syndrome
- Myasthenia gravis
- Pain, numbness, and asymmetrical weakness consistent with a vasculitis syndrome

ADLs = activities of daily living; HIV = human immunodeficiency virus; po = by mouth; TSH = thyroid-stimulating hormone.
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Appendix L. Care Step Pathway: Nephritis (inflammation of the kidneys)

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?
  - » Shortness of breath?
- 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 increased >ULN–1.5 × ULN	Creatinine >1.5–3.0 × baseline; >1.5–3.0 × ULN	Creatinine >3.0 × baseline; > 3.0–6.0 × ULN	Creatinine >6.0 × ULN; life-threatening consequences; dialysis indicated	

☞ *Table continued on the following page*

Appendix L. Care Step Pathway: Nephritis (inflammation of the kidneys; cont.)

Management

Overall Strategy

- Assess for other etiologies such as dehydration (common), infection, and recent IV contrast
- Eliminate potentially nephrotoxic
- 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 and urine protein (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 dosage to 7.5 mg prednisone/day
- Pembrolizumab or nivolumab to be withheld for Grade 2 events
- 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 symptoms improve to baseline followed by slow taper over at least 1 month
  - » Anticipate increase 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 symptom 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

Severe (Grade 3) or Potentially Life-threatening (Grade 4)

- Pembrolizumab to be permanently discontinued for Grade 3 (severe) or Grade 4 (life-threatening) nephritis
- Nivolumab to be withheld for Grade 3 (severe) and permanently discontinued for Grade 4 (life-threatening) serum creatinine elevation
- Consider hospital admission
- 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 (e.g., azathioprine, cyclophosphamide, cyclosporine, infliximab, mycophenolate mofetil)
- Anticipate nephrology consultation will be initiated by provider
- Anticipate that renal biopsy will be considered
- Hemodialysis may be considered

☞ *Table continued on the following page*

Appendix L. Care Step Pathway: Nephritis (inflammation of the kidneys; cont.)

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
- Continue assessing for nephrotoxic medications over the treatment course
- Monitor creatinine and urine protein 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

*Administering Corticosteroids

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

- Taper should consider patient's current symptom profile
- Close follow-up in person or by phone, based on individual need and symptomatology
- Steroids cause indigestion; provide antacid therapy daily as gastric ulcer prevention while on steroids (e.g., proton pump inhibitor or H2 blocker if prednisone dosage is >20 mg/day)
- Review steroid medication side effects: mood changes (angry, reactive, hyperaware, euphoric, manic), increased appetite, interrupted sleep, oral thrush, fluid retention
- Be alert to recurring symptoms as steroids taper down and 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
- If extended steroid use, risk for osteoporosis; initiate calcium and vitamin D supplements

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; NSAIDs = nonsteroidal anti-inflammatory drugs; OTC = over the counter; po = by mouth; PPI = proton pump inhibitor; QOL = quality of life; ULN = upper limit of normal. Copyright © 2019 IO Essentials.