Ipilimumab-Based Therapy

Consensus statement from the faculty of the Melanoma Nursing Initiative on managing adverse events with ipilimumab monotherapy and combination therapy with nivolumab

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BACKGROUND: Ipilimumab (Yervoy®) therapy improves outcomes in patients with resected stage III melanoma, and ipilimumab alone or combined with nivolumab (Opdivo®) does so in those with unresectable or metastatic melanoma. These immunotherapies are associated with immune-related adverse events (irAEs). With prompt recognition and appropriate management, serious sequelae or unnecessary treatment discontinuation can be prevented.

OBJECTIVES: This article presents consensus statements to guide oncology nurses in the recognition and management of irAEs associated with ipilimumab and nivolumab.

METHODS: Members of the Melanoma Nursing Initiative reviewed the current literature and clinical experience regarding nursing interventions related to irAEs associated with ipilimumab or ipilimumab and nivolumab therapy.

FINDINGS: The care step pathways provided represent a proactive, evidence-based, and comprehensive plan to support optimal patient outcomes.

KEYWORDS
CTLA4 inhibitor; immune-related adverse events; ipilimumab; nivolumab; melanoma

DIGITAL OBJECT IDENTIFIER
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MELANOMA OUTCOMES HAVE BEEN DRAMATICALLY ADVANCED by the development of immune checkpoint inhibitors (ICIs), which impede either cytotoxic T lymphocyte–associated antigen 4 (CTLA4) or programmed cell death protein 1 (PD-1) to enhance the patient's immune system recognition and attack on cancer. Ipilimumab (Yervoy®) is a CTLA4 inhibitor that improved survival in phase 3 trials in unresectable stage III and stage IV melanoma (advanced melanoma) (Hodi et al., 2010; Robert et al., 2011). In 2011, the U.S. Food and Drug Administration (FDA) approved ipilimumab for advanced melanoma. Subsequently, ipilimumab was shown to prolong recurrence-free and overall survival as an adjuvant therapy in resected stage III melanoma (Eggermont et al., 2016) and received FDA approval for this indication in 2015. In addition, dual checkpoint blockade with ipilimumab, plus the PD-1 inhibitor nivolumab (Opdivo®), provides longer progression-free survival versus ipilimumab alone in advanced melanoma (Larkin et al., 2015) and was approved for this use in 2014.

Immune checkpoints serve as on- or off-regulators. In particular, CTLA4 and PD-1 act as off, or "brake," mechanisms for the immune system. These pathways are exploited through interruptions to the brake system (i.e., taking the brakes off the immune system through ICIs). Although CTLA4 and PD-1 inhibitors work by sustaining (T-cell) immune responses, anti-CTLA4 tends to act earlier in the process than PD-1 (Boutros et al., 2016). These differences may also account for the divergent efficacy and toxicity profiles of CTLA4 and PD-1 inhibitors when used as monotherapy (Buchbinder & Desai, 2016). In the CheckMate 067 trial by Larkin et al. (2015), the group receiving ipilimumab and nivolumab therapy demonstrated higher response rates as well as increased progression-free survival versus ipilimumab monotherapy. However, the combination of ipilimumab and nivolumab was also associated with a higher proportion of severe toxicity: Fifty-five percent (n = 172) of patients in the combination therapy group experienced a treatment-related grade 3 or 4 adverse event, compared with 27% (n = 85) of those who received ipilimumab and 16% (n = 51) of those who received nivolumab, respectively (Larkin et al., 2015).

Members of the Melanoma Nursing Initiative (MNI) noted that the ipilimumab and nivolumab combination and high-dose ipilimumab adjuvant therapy

are associated with the highest overall immune-related adverse event (irAE) rates and severity compared with other ICI regimens. The irAEs associated with these regimens also tend to have an earlier onset and faster progression versus other ICIs (see Figures 1, 2, and 3) (Boutros et al., 2016). Therefore, hypervigilance is warranted when monitoring patients who are receiving these regimens.

The MNI members convened to define supportive care challenges associated with ipilimumab-based therapy. Drawing from their clinical experience as well as review of the literature, they developed consensus recommendations for nursing care of this population. Recommendations were made in the following areas:

- Administration and dosing, with information on recommended drug holds and discontinuations
- irAE recognition and management

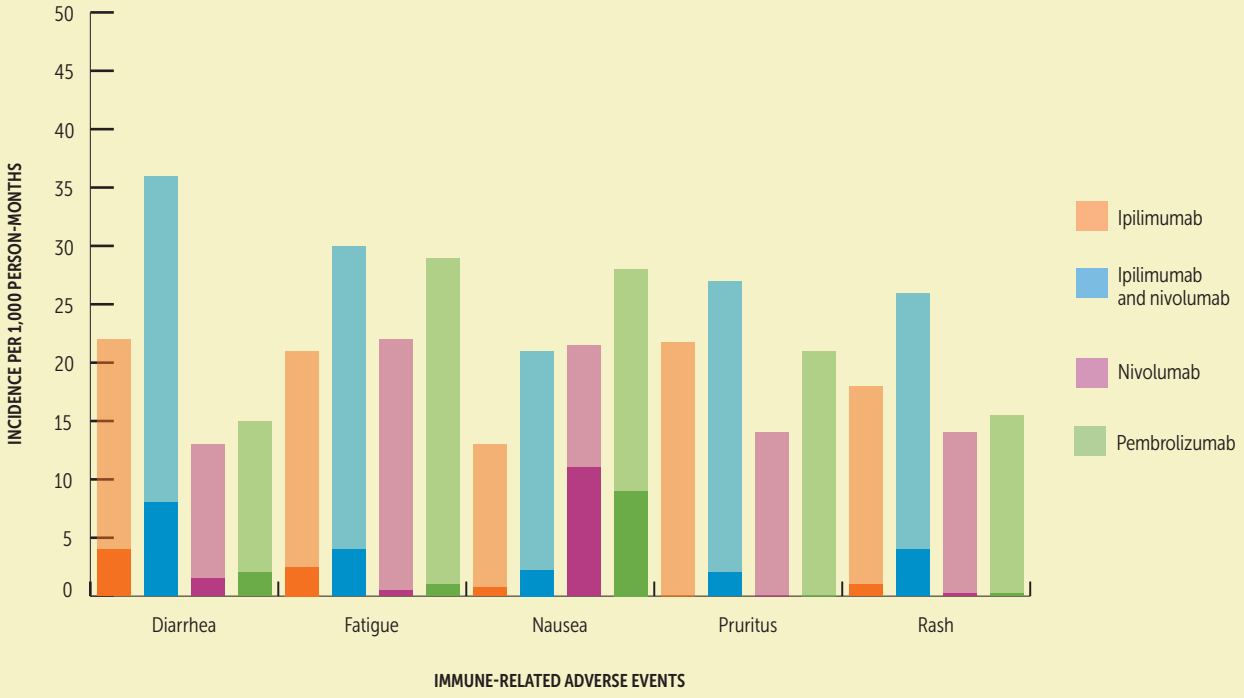
Care step pathways (CSPs) were developed for high-priority irAEs associated with ICIs, for which nursing assessment and care are key in promoting successful outcomes. This article focuses on irAE recognition and management principles specific to ipilimumab-based therapy.

"With the combination therapy, many immune-related adverse events occur even earlier and with greater severity."

Drug Administration and Dosages

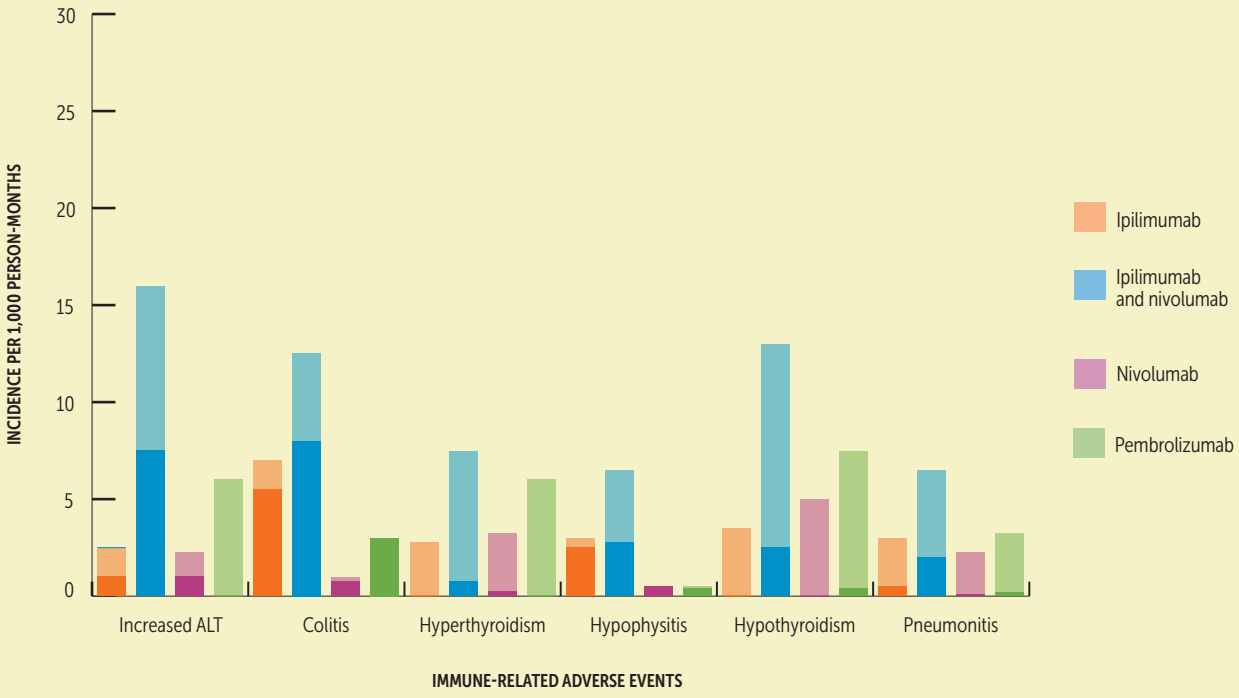
Information on ipilimumab and nivolumab dosing by indication is provided in Table 1 (Bristol-Myers Squibb, 2017a, 2017c). No premedications are given to prevent irAEs. Toxicity management may vary by the specific irAE, and more detail is discussed

FIGURE 1.
MOST COMMON ADVERSE EVENTS WITH IMMUNE CHECKPOINT INHIBITORS



Note. Adverse events of grades 1–2 are represented by lighter shades, and adverse events of grades 3–5 are represented by darker shades.
Note. From "Safety Profiles of Anti-CTLA-4 and Anti-PD-1 Antibodies Alone and in Combination," by C. Boutros, A. Tarhini, E. Routier, O. Lambotte, F.L. Ladurie, F. Carbonnel, . . . C. Robert, 2016, *Nature Reviews Clinical Oncology, 13,* pp. 473–486. Copyright 2016 by Macmillan Publishers Ltd. Adapted with permission.

FIGURE 2.
ADVERSE EVENTS OF SPECIAL INTEREST ASSOCIATED WITH IMMUNE CHECKPOINT INHIBITORS



ALT—alanine aminotransferase
Note. Adverse events of grades 1–2 are represented by lighter shades, and adverse events of grades 3–5 are represented by darker shades.
Note. From "Safety Profiles of Anti-CTLA-4 and Anti-PD-1 Antibodies Alone and in Combination," by C. Boutros, A. Tarhini, E. Routier, O. Lambotte, F.L. Ladurie, F. Carbonnel, . . . C. Robert, 2016, *Nature Reviews Clinical Oncology, 13,* pp. 473–486. Copyright 2016 by Macmillan Publishers Ltd. Adapted with permission.

in the current article's CSPs and tables. Of note, a much higher dose of ipilimumab (10 mg/kg versus 3 mg/kg) and a longer treatment duration are used as adjuvant treatment than are used as monotherapy or in combination therapy in the advanced melanoma setting. A dose-ranging study evaluating doses of 0.3 mg/kg, 3 mg/kg, and 10 mg/kg showed a clear dose-response effect on efficacy and toxicity for ipilimumab (Wolchok et al., 2010). Therefore, greater toxicity associated with the 10 mg/kg ipilimumab dose used for adjuvant therapy versus the 3 mg/kg dose used for metastatic disease may be expected (Eggermont et al., 2016).

Nursing Interventions

Patient Advocacy in Therapy Selection

The best treatment approach in advanced melanoma remains debatable (i.e., whether to use a single agent versus a combination approach and how to sequence agents). Although nurses generally play a supportive role, they also serve as advocates for patient safety when treatment decisions are being made. In this capacity, nurses should assess for and highlight any concerns regarding barriers in physical resources (e.g., transportation, communication tools), as well as in personal support when patients undertake these effective but challenging regimens. Members of the MNI noted that PD-1 inhibitors are used more frequently than ipilimumab monotherapy in the metastatic setting, given the higher response rates and lower percentages of toxicity (Larkin et al., 2015; National Comprehensive Cancer Network [NCCN], 2016; Robert, Schacter, et al., 2015). The efficacy–safety balance becomes a major discussion point when evaluating ipilimumab and nivolumab combination therapy versus PD-1 inhibitor monotherapy in this setting. In a similar way, the use of high-dose ipilimumab in the adjuvant setting is also informed by a benefit–risk discussion because of the potential for toxicities (NCCN, 2016).

General Education

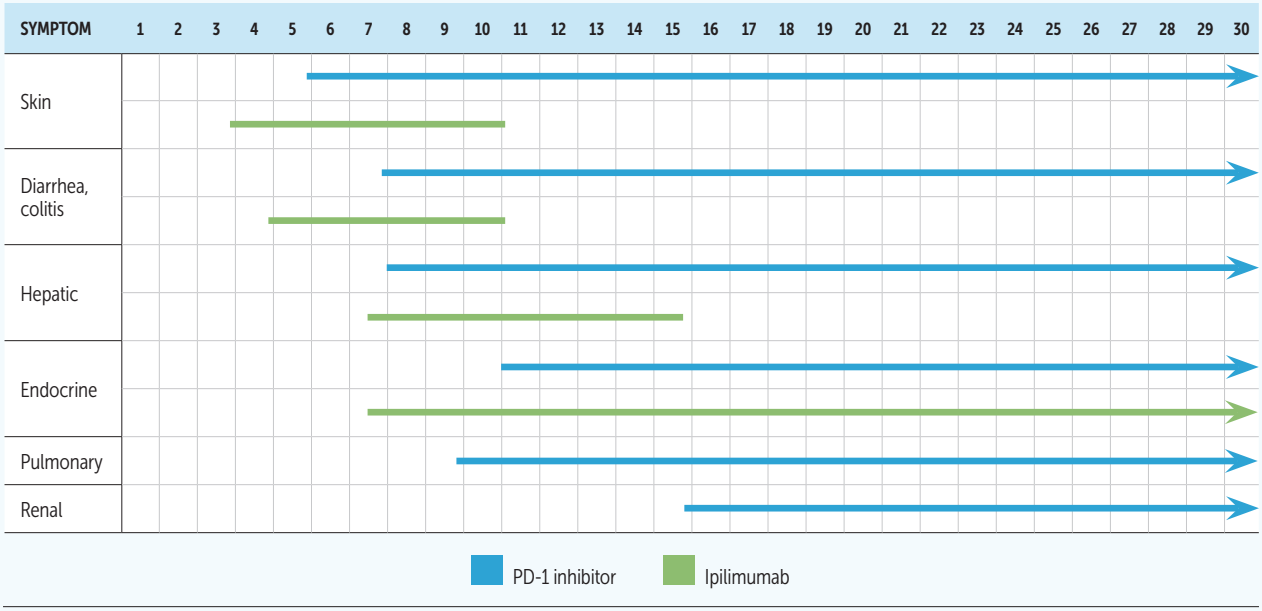
Thorough, individualized, and comprehensible patient education is the critical first step of irAE management. Healthcare providers should emphasize to patients that any changes, even subtle

variations in feeling, could be signs of an irAE and should be reported immediately. This is particularly important for patients who may be concerned about staying on therapy and who may feel the need to endure irAEs. Therefore, nurses need to form a strong partnership with patients and their caregivers to ensure that timely communication occurs. In the authors' experience, patients sometimes encounter signs and symptoms that they think are attributable to the flu or a cold but that represent an irAE. Nurses should further emphasize that, although certain irAEs are more common than others and tend to occur at particular times following treatment initiation, ICIs can potentially affect any organ system or tissue and may occur at any time, including after treatment completion or discontinuation. Within this framework, the importance of obtaining baseline and follow-up testing to aid in irAE detection and diagnosis should be highlighted (Champiat et al., 2016).

Patients should also receive health maintenance information before therapy begins. Women of childbearing age should be counseled to avoid pregnancy because of the potential embryofetal toxicity associated with ICIs; effective birth control should be employed during therapy and for three months after the last dose (Bristol-Myers Squibb, 2017a; Friedman, Proverbs-Singh, & Postow, 2016). In addition, because ipilimumab is administered in the adjuvant setting for as many as three years, issues related to family planning may be highly relevant. Fertility studies have not been performed with ipilimumab (Bristol-Myers Squibb, 2017c). Given the long duration of therapy and the unknown impact on fertility in men and women, the oncology team should have open, candid discussions about family planning with patients of childbearing age and note any potential barriers or contraindications to future goals (Walter, Xu, Paller, Choi, & Woodruff, 2016). A possible recommendation may be referral to a fertility specialist to discuss potential sperm or egg banking as an option. Nurses continue to support the process by reinforcing conversations and addressing patient concerns.

Regarding other aspects of health maintenance, use of a sports team analogy may help the patient to understand the team-based approach employed and the central role of the oncologist. Patients may be counseled that their oncologist will become the quarterback of their care and, therefore, needs to have the picture of everything happening on the field. Patients should consult their oncology team before they receive elective surgery, dental procedures, or other medical interventions; start taking new medications or herbal supplements; or employ complementary modalities. The use of attenuated vaccines has been and continues to be evaluated. Live vaccines (e.g., measles, mumps, and rubella vaccine; varicella vaccine) have not been evaluated in this setting and are usually not advised (Bristol-Myers Squibb, 2017b;

FIGURE 3.
SYMPTOM ONSET AND DURATION (WEEKS)



PD-1—programmed cell death protein 1
Note. Figure shows the time course (median times) of appearance of immune-related adverse events with the PD-1 inhibitor (nivolumab) and ipilimumab (all doses). Combination therapy would generally be expected to produce immune-related adverse events at an earlier onset.
Note. Based on information from Weber et al., 2012, 2017.
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Merck, 2017). Nurses should counsel patients to discuss all immunizations with the oncology team to weigh the benefits and risks on an individual basis.

Oncology nurses should ensure that patients are aware of educational and financial resources for their therapies and how to access them (see Figure 4). In the experience of the MNI members, drug-specific wallet cards, which identify signs and symptoms that should be immediately reported to the treating oncologist or other members of the healthcare team, are particularly helpful. Patients should be encouraged to carry the card with them, even paperclipping their wallet card to their insurance card; by doing so, whenever they need to show their insurance card, they can share information about their immunotherapy regimen as well. Wallet cards not only serve as ready guides for notable signs and symptoms potentially reflective of an irAE but also provide relevant information to other healthcare providers, such as emergency department personnel, to improve patient care.

Care Step Pathways

In general, irAEs observed with ipilimumab are similar to those associated with PD-1 inhibitor therapy, although they tend to occur more frequently and more severely. Ipilimumab acts early in the immunologic cascade, so many inflammatory AEs can occur. With the combination therapy, many irAEs occur even earlier and with greater severity. Optimal irAE management depends on early recognition, followed by appropriate strategies to minimize their impact (Boutros et al., 2016; Villadolid & Amin, 2015). Once identified, irAEs are typically managed symptomatically and/or with selective use of corticosteroids or other immunosuppressives, combined with withholding or discontinuation of ICIs, depending on the severity or persistence of the irAE (Boutros et al., 2016; Villadolid & Amin, 2015). Referral to an organ specialist is often warranted, particularly for more serious or severe irAEs or for those that the healthcare provider is not experienced in managing, such as endocrinopathies. With prompt recognition and appropriate treatment, some irAEs are reversible; endocrinopathies are an exception and are generally managed with lifelong hormone replacement therapy (HRT). With respect to corticosteroid use, some patients may be concerned that because corticosteroids are immunosuppressive, they may interfere with ICI efficacy. Nurses should assure patients that studies indicate that ICI efficacy is not adversely affected by corticosteroids or treatment of irAEs (Horvat et al., 2015; Weber et al., 2015).

Each CSP represents a notable irAE associated with ICIs and incorporates essential components of the nursing assessment specific to that irAE. Look, listen, and recognize categories within the nursing assessment section direct the nurse to a specific set of symptom-related queries to ask the patient and/or caregiver and highlight additional information to be considered and reviewed as part of the nursing assessment. Data obtained from this assessment will guide appropriate management strategies. Wherever possible, grading for the specific AE is provided within the pathway based on the National Cancer Institute's (2010) Common Terminology Criteria for Adverse Events (CTCAE). However, for irAEs for which management is largely directed based on laboratory data (such as thyroid disorders and diabetes), the authors used standard cutpoint criteria rather than the CTCAE criteria.

Each CSP describes overall management strategies as well as nursing-specific interventions. Where applicable, interventions for at-risk groups along with strategies specific to each AE grade are listed, including dose holds and discontinuations. Patient counseling, recommendations for additional care, and referral to specialty or ancillary care providers are included in the management section, as appropriate.

Some general principles inform management strategies across all the CSPs. Corticosteroid dosages are detailed in the CSPs, and these high dosages are often split into two daily doses. Corticosteroids should be gradually tapered (usually for at least a month) to avoid rebound symptoms. Methylprednisolone dosepaks are used by some providers, but are often not sufficient

APPENDIXES A–K.
CARE STEP PATHWAYS

Care step pathways for Appendixes A–K in Madden and Hoffner (2017) and McGettigan and Rubin (2017) can be found on pp. 52–75. A reference list for Appendixes A–K can be found on p. 71.

- **Appendix A:** Care step pathway for management of skin toxicities, p. 52
- **Appendix B:** Care step pathway for management of gastrointestinal toxicity: Diarrhea and colitis, p. 54
- **Appendix C:** Care step pathway for management of mucositis and xerostomia, p. 57
- **Appendix D:** Care step pathway for management of hepatotoxicity: Immunotherapy-induced inflammation of liver tissue, p. 59
- **Appendix E:** Care step pathway for management of hypophysitis: Inflammation of pituitary gland, p. 62
- **Appendix F:** Care step pathway for management of thyroiditis: Inflammation of thyroid gland, p. 64
- **Appendix G:** Care step pathway for management of type 1 diabetes mellitus: Immune destruction of beta cells in pancreas, p. 66
- **Appendix H:** Care step pathway for management of pneumonitis: Inflammation of lung alveoli, p. 67
- **Appendix I:** Care step pathway for management of arthralgias and arthritis, p. 69
- **Appendix J:** Care step pathway for management of neuropathy: Motor or sensory nerve impairment or damage, p. 72
- **Appendix K:** Care step pathway for management of nephritis: Inflammation of the kidneys, p. 74

TABLE 1.
DOSING RECOMMENDATIONS FOR IPILIMUMAB-BASED TREATMENT OF MELANOMA

DRUG REGIMEN	INDICATION	RECOMMENDED DOSAGE AND ADMINISTRATION
Ipilimumab	Advanced melanoma	■ 3 mg/kg administered via IV for 90 minutes every three weeks for a maximum of four doses ■ In the event of toxicity, doses may be delayed, but all treatment should be administered within 16 weeks of the first dose.
Ipilimumab (adjuvant for stage III melanoma)	Adjuvant for resected stage III melanoma	■ 10 mg/kg administered via IV for 90 minutes every three weeks for four doses, followed by 10 mg/kg every 12 weeks for as many as three years ■ In the event of toxicity, doses are omitted, not delayed.
Nivolumab	Advanced melanoma	■ 240 mg (flat dose) administered as an IV infusion for 60 minutes every two weeks until disease progression or unacceptable toxicity
Nivolumab and ipilimumab	Advanced melanoma	■ Nivolumab 1 mg/kg administered as an IV infusion for 60 minutes, followed by ipilimumab 3 mg/kg on the same day every three weeks for four doses ■ Recommended subsequent dose of nivolumab, as a single agent, is 240 mg administered as an IV infusion for 60 minutes every two weeks until disease progression or unacceptable toxicity

Note. Based on information from Bristol-Myers Squibb, 2017a, 2017c.

to reduce higher grade inflammatory reactions resulting from the ICIs. Gastric prophylaxis with a proton pump inhibitor or H_2 blocker should be considered when initiating high-dose corticosteroids. Patients should be educated to take their steroid dose with food. In addition, antimicrobial prophylaxis should be considered for patients prescribed high-dose steroids, particularly for those patients requiring extended therapy (greater than 20 mg per day for more than one month) (Limper et al., 2011).

Common Immune-Related Adverse Events

SKIN TOXICITIES

Maculopapular rash and pruritus (without rash) are the most common irAEs associated with ICI treatment and are usually the first to appear (Dadu, Zobniw, & Diab, 2016; Friedman et al., 2016). Pruritic rash is more common in ipilimumab-based regimens. Rash with or without pruritus is usually mild to moderate and can be effectively managed with prompt treatment (Boutros et al., 2016; Dadu et al., 2016). Appendix A provides a detailed CSP for ICI-emergent rash or pruritus.

Nurses must educate patients about the cutaneous irAEs, implement self-care strategies in at-risk individuals, and minimize the severity of irAEs that do develop. Self-care strategies, such as gentle skin care and use of moisturizers and sun-protective techniques, are important early interventions for rash and pruritus, particularly in at-risk patients (those with preexisting conditions, such as dermatitis or xerosis). If patients develop skin-related toxicities, the nurse should grade the toxicity, provide appropriate supportive care interventions, and work as part of the team for management. The role of treatment holds and the use of topical and oral steroids are discussed in the CSP. Rarely, skin toxicities can progress and become severe or life-threatening; consequently, ongoing vigilance is necessary to promptly recognize red flags, such as extensive or rapidly progressive rash, oral involvement, or other indicators of Stevens-Johnson syndrome or toxic epidermal necrolysis, which represent medical emergencies that typically require hospitalization.

GASTROINTESTINAL TOXICITIES

Gastrointestinal toxicities are the second most common irAEs observed with ICI therapy, and they range from mild diarrhea to severe colitis and intestinal perforation, which can lead to death (Cramer & Bresalier, 2017; Dadu et al., 2016; Gupta, De Felice, Loftus, & Khanna, 2015). Diarrhea without symptoms of colitis is the most common gastrointestinal presentation with ICIs (Cramer & Bresalier, 2017; Dadu et al., 2016; Gupta et al., 2015). Abdominal pain, together with mucus and/or blood in the stool, is suggestive of colitis rather than simple diarrhea (Gupta et al., 2015). In an analysis of ICI irAEs, ipilimumab-induced colitis was the most common cause of fatal irAEs across clinical trials (De Velasco et al., 2017). The colitis associated with high-dose (10 mg/kg) ipilimumab and the combination regimen is generally more severe and has a quicker onset than that associated with PD-1 inhibitor monotherapy. As a result, early reporting from patients is critical, and diligence is required in the clinic to recognize and manage this irAE early.

Appendix B provides a detailed CSP for ICI-emergent gastrointestinal toxicities. Nurses play a vital role in the early identification and grading of these toxicities by comparing baseline measures of bowel movements to current status. They may arrange a laboratory workup and/or office visit, when appropriate. Non-ICI–related causes of diarrhea need to be ruled out to ensure proper treatment (Dadu et al., 2016; Gupta et al., 2015). Because colitis can progress to severe or life-threatening forms, hospitalization is often required with gastrointestinal consultation, and surgical consultation is needed if peritoneal signs are noted (e.g., poor appetite, nausea, abdominal pain or tenderness aggravated

by movement, distension) and perforation is suspected. For diarrhea that is moderate to severe, corticosteroids are key to managing symptoms. However, if a patient is not responsive to corticosteroid therapy, the addition of infliximab at 5 mg/kg may be considered, followed by slow taper until diarrhea symptoms resolve (Dadu et al., 2016).

ICIs may also adversely affect the proximal portion of the gastrointestinal system, causing inflammation of the oral mucosa and leading to mucositis and xerosis. Appendix C provides a detailed CSP for ICI-emergent mucositis and xerostomia. These irAEs may be easily overlooked but can negatively affect patients' quality of life. Nurses need to recognize the immune-related causation, which leads to a different management strategy versus that used for mucositis associated with chemotherapy.

HEPATOTOXICITY

ICIs commonly produce hepatitis, which typically manifests as elevated alanine aminotransferase or aspartate aminotransferase levels (Dadu et al., 2016; Friedman et al., 2016). Liver transaminase elevations are observed less frequently with ICIs than skin or gastrointestinal toxicities, but relatively high rates have been reported with the ipilimumab and nivolumab combination or high-dose ipilimumab therapy (Eggermont et al., 2015; Larkin et al., 2015). Asymptomatic, improperly managed

FIGURE 4.
NURSE AND PATIENT/CAREGIVER RESOURCES TO SUPPORT IPILIMUMAB-BASED TREATMENT OF MELANOMA

ADVERSE EVENTS AND MANAGEMENT AIDS (IPILIMUMAB)

Common and serious side effects (adjuvant for stage III melanoma)
- www.yervoy.com/adjuvant/side-effects-of-yervoy

Common and serious side effects (metastatic melanoma)
- www.yervoy.com/metastatic/select-side-effects-of-yervoy

Medication guide
- http://packageinserts.bms.com/medguide/medguide_yervoy.pdf

Patient wallet card
- http://bit.ly/2tovya9

Risk Evaluation and Mitigation Strategy
- http://bit.ly/2s1oko7

ADVERSE EVENTS AND MANAGEMENT AIDS (IPILIMUMAB AND NIVOLUMAB)

Downloadable resources
- http://bit.ly/2tomMbV

Patient wallet card
- http://bit.ly/2tovya9

DRUG ACCESS AND FINANCIAL RESOURCES

Oncology support services (benefit investigation, prior authorization, claims appeal, patient financial assistance, charitable foundation lookup tool, access to care services; for nurses)
- www.bmsaccesssupport.bmscustomerconnect.com

Understanding the reimbursement process, determining coverage, and investigating options for financial support (for patients and caregivers)
- www.bmsaccesssupport.bmscustomerconnect.com/patient

GENERAL PRODUCT INFORMATION (IPILIMUMAB)

Adjuvant for stage III melanoma: Mechanism of action, clinical trial results, and dosing and administration
- www.yervoy.com/servlet/servlet.FileDownload?file=00Pi000000ae0NXEAY

Metastatic melanoma: Mechanism of action, clinical trial results, and dosing and administration
- www.yervoy.com/servlet/servlet.FileDownload?file=00Pi000000TVtP6EAL

GENERAL PRODUCT INFORMATION (IPILIMUMAB AND NIVOLUMAB)

Mechanism of action, clinical trial results, and dosing and administration
- www.opdivo.com/servlet/servlet.FileDownload?file=00Pi000000o0a9ZEAQ

GENERAL SUPPORT (IPILIMUMAB)

Adjuvant for stage III melanoma: Patient and caregiver support materials
- www.yervoy.com/adjuvant/yervoy-materials

Metastatic melanoma: Patient and caregiver support materials
- www.yervoy.com/metastatic/yervoy-materials

Resources related to cancer and melanoma
- www.yervoy.com/metastatic/getting-personal-support

Support resources and personalized care counselor support
- www.patientsupport.bmscustomerconnect.com/yervoywithyou
- 1-855-4YERVOY

GENERAL SUPPORT (IPILIMUMAB AND NIVOLUMAB)

Downloadable resources
- http://bit.ly/2tomMbV

Living with melanoma
- http://bit.ly/2shoPP4

Resources related to cancer and melanoma
- http://bit.ly/2sm0hQd

PATIENT ADVOCACY AND NURSE SUPPORT

Nurse on Call (for patients and caregivers)
- www.aimatmelanoma.org/living-with-melanoma/nurse-on-call
- 1-877-246-2635

Resources (for patients and caregivers)
- http://bit.ly/2spYXyW

Symposiums (for patients and caregivers)
- http://bit.ly/2sAyFZ9

Toolkits for promoting adherence and managing adverse events, downloadable patient materials, and community nurse portal (for nurses)
- www.themelanomanurse.org

TABLE 2.
MANAGEMENT OF ADVERSE EVENTS (AEs) ASSOCIATED WITH IPILIMUMAB-BASED THERAPY

VARIABLE	COMMON SYMPTOMS	AGENT	COMMON MANAGEMENT AND ANTICIPATORY GUIDANCE
Acute respiratory distress syndrome	Severe shortness of breath; dyspnea or rapid breathing; hypotension; confusion; extreme fatigue	Ipilimumab	Serious condition requiring hospitalization and expert care, including supplemental oxygen, often mechanical ventilation, and fluid management
Anorexia	Decreased appetite	Ipilimumab, nivolumab	Monitor weight; query patients about appetite and eating habits; advise dietary modification if necessary (should improve with time). Anticipate standard dose holds and discontinuations[a,b].
Cardiotoxicity: cardiomyopathy, myocarditis, heart failure	Dyspnea; edema; fatigue; chest pain; arrhythmias; abdominal pain or ascites	Ipilimumab, nivolumab	Monitor weight; changes in breathing; extremity edema; chest, back, arm, and jaw pain; and pressure sensation in chest. Recommend electrocardiogram and echocardiogram; make stress test cardiology referral; administer 2 mg/kg prednisone; discontinue therapy.
Constipation and abdominal pain	Infrequent stools; difficulty stooling; abdominal pain	Nivolumab	Increase fluid, fiber, and laxatives; consider appropriate testing to evaluate bowel obstruction. Anticipate standard dose holds and discontinuations for grade 3 or 4 (constipation with manual evacuation indicated, severe abdominal pain, or life-threatening consequences)[b].
Embryo-fetal toxicity	–	Ipilimumab, nivolumab	Advise women of reproductive potential of risk to fetus and to use effective contraception during treatment and for three months after ipilimumab and five months after nivolumab is discontinued. Advise patients to immediately notify healthcare provider if they suspect pregnancy while undergoing therapy.
Encephalitis	Headache; fever; tiredness; confusion; memory problems; sleepiness; hallucinations; seizures; stiff neck	Ipilimumab, nivolumab	For new-onset (grade 2 or 3) moderate to severe symptoms, rule out infectious or other causes, consult neurologist, and obtain brain magnetic resonance imaging and lumbar puncture. For ipilimumab, anticipate standard dose holds and discontinuations; administer corticosteroids at a dosage of 1–2 mg/kg per day prednisone equivalents or 2–4 mg/kg if necessary. For nivolumab, withhold for new-onset grade 3 or 4 moderate to severe neurologic symptoms; permanently discontinue for immune-mediated encephalitis.
Fatigue	Feeling tired; lack of energy	Ipilimumab, nivolumab	Query patients regarding energy level; evaluate possible contributory factors, including infection, disease progression, and hematologic and biochemical abnormalities; provide standard supportive care. Anticipate standard dose holds and discontinuations[a,b].
Headache	Head pain	Ipilimumab	Rule out brain metastases, encephalitis, and hypophysitis; otherwise, provide standard supportive care (should improve with time). Anticipate standard dose holds and discontinuations[a].
Infusion reaction	Chills and shaking; itch; flushing; difficulty breathing; hypotension; fever	Ipilimumab, nivolumab	For ipilimumab or nivolumab, with mild to moderate symptoms (grade 1 or 2), interrupt or slow rate of infusion and monitor to recovery; with severe to life-threatening symptoms (grade 3 or 4), discontinue ipilimumab or nivolumab, manage anaphylaxis via institutional protocol, and monitor. Premedication with an antipyretic and antihistamine may be considered.
Insomnia	Difficulty falling or staying asleep	Ipilimumab	Standard sleep hygiene; prescription medications if needed (should improve with time). Anticipate standard dose holds and discontinuations[a].
Nausea and vomiting	Vomiting; queasiness; left or right upper quadrant pain	Ipilimumab, nivolumab	May indicate hepatotoxicity; check liver function tests, as well as lipase and amylase; provide standard supportive care. Anticipate standard dose holds and discontinuations[a,b].
Ocular: conjunctivitis, blepharitis, episcleritis, iritis, ocular myositis, scleritis, uveitis	Blurry vision, double vision, or other vision problems; eye pain or redness	Ipilimumab	Encourage patient to report any eye symptoms immediately; obtain ophthalmology referral. Anticipate standard dose holds and discontinuations[a].
Pyrexia	Elevated body temperature	Ipilimumab, nivolumab	Provide standard supportive care. Anticipate standard dose holds and discontinuations[a,b].

Continued on the next page

TABLE 2. *(CONTINUED)*
MANAGEMENT OF ADVERSE EVENTS (AEs) ASSOCIATED WITH IPILIMUMAB-BASED THERAPY

VARIABLE	COMMON SYMPTOMS	AGENT	COMMON MANAGEMENT AND ANTICIPATORY GUIDANCE
Rhabdomyolysis	Pain; muscle weakness; vomiting; confusion; tea-colored urine	Ipilimumab, nivolumab	Administer IV fluids and corticosterioids (check for elevated anti-striated muscle titer). Anticipate standard dose holds and discontinuations[a,b].
Upper respiratory tract infection	Cough; runny nose; sore throat; nasal breathing	Nivolumab	Provide standard supportive care. Anticipate standard dose holds and discontinuations[b].

[a] For ipilimumab, withhold for any moderate (grade 2) AE, and resume treatment when AE returns to grade 0 or 1; permanently discontinue for any severe or life-threatening (grade 3 or 4) AE, persistent grade 2 AE lasting six or more weeks, or inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day.
[b] For nivolumab, withhold for any severe (grade 3) AE, and resume treatment when AE returns to grade 0 or 1; permanently discontinue for any life-threatening (grade 4) AE, persistent grade 2 or 3 AE lasting 12 or more weeks, any severe (grade 3) AE that recurs, or when 10 mg or more prednisone or equivalent is required per day for more than 12 weeks.
Note. Based on information from Bilen et al., 2016; Bristol-Myers Squibb, 2017a, 2017c; Heinzerling et al., 2016; Hottinger, 2016; Inadomi et al., 2016; Kanameishi et al., 2016; Kong et al., 2016; Spain et al., 2016; Tabchi et al., 2016; U.S. Food and Drug Administration, 2012; Wanchoo et al., 2017; Zimmer et al., 2016.

hepatic irAEs can lead to mortality (Dadu et al., 2016). Appendix D provides a detailed CSP for ICI-emergent hepatotoxicity. The authors recommend that nurses closely monitor liver function tests (LFTs) in patients receiving combination therapy. LFTs are generally warranted prior to each immunotherapy dose. Transaminase grading may guide the frequency of LFT checks. Given the vital importance and complex functionality of the liver, distinguishing between true organ dysfunction versus immune-mediated issues can be difficult (De Velasco et al., 2017). Consequently, consultation with a hepatologist or gastroenterologist should be considered. A liver biopsy may be necessary to differentiate autoimmune toxicity from other causes of liver injury. Management strategies for moderate to life-threatening hepatotoxicity are high-dose corticosteroids at 1–2 mg/kg. If LFTs remain elevated and refractory to steroids, additional immunosuppression may be considered with the use of mycophenolate mofetil at 500–1,000 mg by mouth every 12 hours until LFTs are stable or declining. Medications should be tapered slowly until resolution of hepatitis (Dadu et al., 2016). Ensuring adherence to the mycophenolate regimen is essential in providing optimal outcomes for these patients.

Rarer But Serious Immune-Related Adverse Events

ENDOCRINOPATHIES

Endocrinopathies associated with ICIs occur because the overactive immune system damages endocrine organs, mimicking the autoimmune process. Endocrinopathies are less common than skin or gastrointestinal irAEs, but they can have serious consequences if not recognized and properly treated (Byun, Wolchok, Rosenberg, & Girotra, 2017). They include hypophysitis, thyroiditis, and type 1 or insulin-dependent diabetes mellitus (Dadu et al., 2016; Friedman et al., 2016). A range of endocrine organs can be affected, including the pituitary, thyroid, pancreas, and adrenal glands. Although relatively rare, these endocrinopathies can lead to serious sequelae. Hypophysitis may lead to various hormone deficiencies, including central hypothyroidism, hypogonadism, and/or adrenal insufficiency. Similarly, thyroiditis can lead to hyperthyroidism, often followed by hypothyroidism. Nurses should be aware that endocrinopathies often present with vague symptoms (e.g., fatigue, headache, depression) that require further evaluation. They should discuss with patients, at the onset, that ICIs typically produce endocrine conditions requiring lifelong HRT. Patients are usually more willing to accept ICI therapy when they understand they can generally lead normal lives with HRT.

Appendixes E and F provide detailed CSPs for ICI-emergent hypophysitis and thyroiditis, respectively. Particularly when addressing hypophysitis, the nurse should help facilitate collaborative management with an experienced endocrinologist to properly address the challenging diagnostic requirements for this condition. Such collaboration represents the best approach to care, although some oncology practices will become more independent in their management of these irAEs over time.

Type 1 diabetes mellitus is a much rarer endocrinopathy linked with ICI therapy (Dadu et al., 2016; Friedman et al., 2016), but it can be disconcerting for patients, given the potential serious consequences. The condition is caused by autoimmune destruction of pancreatic beta cells (Chae et al., 2017) and is a permanent condition managed with insulin therapy. Nurses play an essential role in educating patients regarding this potential irAE, monitoring laboratory tests and patient symptoms, and ensuring prompt and comprehensive management if the patient develops type 1 diabetes mellitus. Appendix G provides a detailed CSP for ICI-emergent type 1 diabetes mellitus.

PNEUMONITIS

Pneumonitis is a rare but potentially fatal irAE. Like endocrinopathies, pneumonitis tends to occur later than most other ICI-associated irAEs; however, like all irAEs, pneumonitis may occur

and should be anticipated at any time. Highest rates are observed with ipilimumab and nivolumab combination therapy (Dadu et al., 2016; Friedman et al., 2016). This condition is frequently diagnosed based on imaging, such as follow-up computed tomography tests, because it is often asymptomatic. Nurses should consider a referral to a pulmonary specialist for patients presenting with nonspecific pulmonary symptoms, such as upper respiratory tract infection, new or persistent cough, or dyspnea. In early phases, pneumonitis may present as dyspnea on exertion, which the nurse may evaluate through pulse oxygen monitoring in the clinic. Patients who develop abnormalities in such testing can be considered for further radiologic testing. Appendix H provides a detailed CSP for ICI-emergent pneumonitis.

Easily Overlooked and Other Immune-Related Adverse Events

ICIs can potentially affect any body organ or tissue. Other irAEs have been reported with ipilimumab and/or nivolumab, highlighting the wide range of affected tissues (Bristol-Myers Squibb, 2017a, 2017c). Of particular importance are those affecting the musculoskeletal, nervous, and renal systems. Appendix I provides a detailed CSP for ICI-emergent arthralgias and arthritis, which were reported in more than 10% of patients receiving ipilimumab and nivolumab combination therapy (Cappelli, Shah, & Bingham, 2017; Larkin et al., 2015). If not anticipated, these irAEs are easily overlooked or not associated with ICIs. Permanent joint damage may occur without treatment, and referral to a rheumatologist is sometimes warranted (Cappelli, Naidoo, Bingham, & Shah, 2017). Arthralgias or arthritis often require more prolonged anti-inflammatory treatment than other irAEs. However, the authors reported some cases in which low-dose prednisone can have a major effect on quality of life, particularly in older adults.

Appendix J provides a detailed CSP for ICI-emergent neuropathy, specifically motor or sensory nerve impairment or damage. ICIs can cause rare but serious and life-threatening neurologic irAEs, including rapidly progressing encephalitis. For example, encephalopathy can be initially mistaken for an endocrinopathy before rapidly progressing from headache to confusion to coma. Prompt referral to a neurologist for further evaluation is warranted. Many of the symptoms for the irAEs overlap (e.g., headache), and patients often provide only vague descriptions. Therefore, accurate diagnosis can be delayed, leading to poorer outcomes. Being aware of the range of toxicities that are possible is important, and immune dysfunction should be considered for every complaint or symptom presentation.

Appendix K provides a detailed CSP for ICI-emergent nephritis. Nurses should make sure that patients are monitored for elevated serum creatinine before and periodically during ICI therapy and referred for appropriate treatment when needed. Table 2 lists other AEs reported with ipilimumab and/or nivolumab treatment that may be directly related to the immune effects of these agents as well as recommended management strategies.

Immunotherapy-induced cardiotoxicity, albeit rare, has been noted to have fatal outcomes in a small number of patients who developed myocarditis or cardiomyopathy (Heinzerling et al., 2016; Johnson et al., 2016). This area is gaining increasing awareness and attention as an irAE. Cardiotoxicity should be considered in patients reporting vague or atypical symptoms, particularly those that are cardiorespiratory in nature (e.g., shortness of breath, weakness, edema). Patients suspected of experiencing a cardiotoxicity should be evaluated immediately (Heinzerling et al., 2016; Johnson et al., 2016).

IMPLICATIONS FOR PRACTICE

- Stress to patients the importance of immediately reporting any changes in their health status to the medical team after starting checkpoint inhibitor therapy.
- In collaboration with the rest of the clinical team, develop a list of knowledgeable specialists to enlist for collaborative care when patients experience organ-specific immune-related adverse events (irAEs).
- Maintain hypervigilance in monitoring for irAEs with ipilimumab and nivolumab combination therapy because they can progress to severe or life-threatening conditions if not recognized early and managed appropriately.

Conclusion

Ipilimumab-based therapy (high-dose adjuvant monotherapy, ipilimumab monotherapy, or ipilimumab and nivolumab combination therapy for advanced disease) improves survival outcomes in patients with melanoma. However, ipilimumab monotherapy and combination therapy produce irAEs unlike those of traditional or newer targeted treatments and at higher rates and severity than with ICI monotherapy. Optimal clinical outcomes in these patient populations depend, in part, on early detection and management of ipilimumab-related irAEs.

Oncology nurses can have a positive impact on outcomes by educating patients about the importance of immediately reporting changes in health status, providing patient support throughout the treatment process, assessing patient adherence and understanding of the dosing regimen, regularly evaluating patient status and potential symptoms, and serving as a liaison among the patient, the medical team, and consulting specialists. By familiarizing themselves with the CSPs presented in this article, nurses will be well prepared to provide the comprehensive patient assistance and support needed to maximize treatment outcomes.

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APPENDIX A.
CARE STEP PATHWAY FOR MANAGEMENT OF 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, preexisting skin issues (e.g., psoriasis), and wounds?
- Laboratory abnormalities consistent with other etiologies (e.g., eosinophils on complete blood count, liver function abnormalities)

GRADING TOXICITY: MACULOPAPULAR RASH (MORBILLIFORM RASH)

A disorder characterized by the presence of macules (flat) and papules (elevated); frequently affects 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 and papules covering less than 10% BSA, with or without symptoms (e.g., pruritus, burning, tightness)	■ Macules and papules covering 10%–30% BSA, with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADLs	■ Macules and papules covering more than 30% BSA, with or without associated symptoms; limiting self-care ADLs; skin sloughing covering less than 10% BSA	■ Papules and pustules covering any percentage of BSA, with or without symptoms, and associated with superinfection requiring IV antibiotics; skin sloughing covering 10%–30% BSA	

GRADING TOXICITY: PRURITUS

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 or crusts); limiting instrumental ADLs	■ Intense or widespread; constant; limiting self-care ADLs or sleep		

MANAGEMENT

Overall strategy
- Assess for other etiology of rash: Ask patient about new medications, including herbals, supplements, alternative or complementary therapies, and lotions.

ADLs—activities of daily living; BSA—body surface area

Note. Based on information from Bristol-Myers Squibb, 2017a, 2017b; Champiat et al., 2016; Dadu et al., 2016; Fecher et al., 2013; Friedman et al., 2016; Kähler et al., 2016; Kumar et al., 2017; Merck, 2017; Naidoo et al., 2015; National Cancer Institute, 2010; Spain et al., 2016; U.S. Food and Drug Administration, 2012.

MANAGEMENT BY GRADE

Intervention (at-risk patients)

- Advise gentle skin care.
  - ☐ Avoid soap. Instead, use nonsoap cleansers that are fragrance- and dye-free; use mild soap on the axillae, genitalia, and feet.
  - ☐ Daily applications of nonsteroidal 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 and 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 nonsteroidal 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 and family to call clinic with any sign of worsening rash or symptoms. Anticipate office visit for evaluation.
- Assess patient and 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 (0.5–1 mg/kg per day) and oral antihistamines and oral antipruritics to be used
- Consider dermatology consultation.
- Patient education
  - ☐ Proper administration of oral corticosteroids (take with food and early in the day; concomitant medications may be prescribed, including H_2 blocker and antimicrobial prophylaxis)
- Advise vigilant skin care.
  - ☐ Gentle skin care
  - ☐ Tepid and oatmeal baths
- Advise strict sun protection.
- Assess patient and 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 Stevens-Johnson syndrome or toxic epidermal necrolysis
- Ipilimumab to be discontinued for any grade 3 or 4 event, and nivolumab for grade 4 rash or confirmed Stevens-Johnson syndrome or toxic epidermal necrolysis
- Pembrolizumab or nivolumab to be discontinued for any grade 3 or 4 event that recurs or persists for 12 or more weeks, or for inability to reduce steroid dose to 10 mg or less prednisone or equivalent within 12 weeks
- Anticipate hospitalization and initiation of IV corticosteroids (1.5–2 mg/kg per day; divided doses).
- Anticipate dermatology consultation with or without 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 and muscle atrophy
- Assess patient and 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 (more than 50% BSA) or rapidly progressive
- Oral involvement
- Concern for suprainfection

APPENDIX B.

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

Recognize

- Serum chemistry and hematologic abnormalities
- Infectious versus 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)

- Increase of less than four stools per day over baseline
- Mild increase in ostomy output compared to baseline

Grade 2 (moderate)

- Increase of four to six stools per day over baseline
- Moderate increase of output in ostomy compared to baseline

Grade 3 (severe)

- Increase of seven or more stools per day over baseline; incontinence
- Hospitalization indicated
- Severe increase in ostomy output compared to 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)

GRADING TOXICITY: 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

Overall strategy

- Rule out infectious, noninfectious, and disease-related etiologies.

MANAGEMENT BY GRADE

Grade 1 (mild)

- May continue immunotherapy
- Diet modifications (very important)
  - ☐ Institute bland diet; decrease fiber, uncooked foods and vegetables, red meats, fats, dairy, oil, caffeine, alcohol, and sugar.

Grade 2 (moderate)

- Send stool sample for *Clostridium difficile* testing, culture, and ova and parasite examination.
- Immunotherapy to be withheld until grade 0 or 1 or patient's baseline (ipilimumab, pembrolizumab, nivolumab)
- Provide antidiarrheals: loperamide (Imodium®) or diphenoxylate and atropine (Lomotil®).
- If upper or lower gastrointestinal symptoms persist for more than five to seven days, oral steroids should be started (prednisone or equivalent 0.5–1 mg/kg per day).
  - ☐ After control of symptoms, a steroid* taper of four or more weeks will be initiated.
- Immunotherapy to be discontinued if grade 2 symptoms persist for six or more weeks (ipilimumab) or for 12 or more weeks (pembrolizumab, nivolumab), or for inability to reduce steroid dose to 7.5 mg or less (ipilimumab) or 10 mg or less prednisone or equivalent (pembrolizumab, nivolumab) within 12 weeks
- Diet modifications
  - ☐ Institute bland diet low in fiber, residue, and fat (BRAT [Bananas, Rice, Applesauce, Toast] diet).
  - ☐ Decrease fiber, uncooked foods and vegetables, red meats, fats, dairy, oil, caffeine, alcohol, and sugar.
  - ☐ Avoid laxatives or stool softeners.
  - ☐ Advance diet slowly as steroids are tapered*, and assess for loose or liquid stool for several days or longer.
- (Moderate) persistent or relapsed symptoms with steroid* taper
  - ☐ Consider gastroenterology consultation for possible intervention (flexible sigmoidoscopy, colonoscopy, endoscopy).
  - ☐ IV steroids* to be started at 1 mg/kg per day
  - ☐ Immunotherapy to be held until grade 0 or 1
  - ☐ Control symptoms, then steroid* taper of four or more weeks
  - ☐ Recurrent diarrhea is more likely when treatment is restarted.

Grades 3–4 (severe or life-threatening)

- Onset
  - ☐ Continued diet modification, antidiarrheals, 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
- Doses of steroids* to be increased
  - ☐ 1–2 mg/kg prednisone or equivalent per day; methylprednisolone (Solu-Medrol®) 1 g IV daily (divided doses)
- Hospitalization
- Gastrointestinal consultation
- Assess for peritoneal signs and perforation (nothing by mouth and abdominal x-ray, surgical consultation when necessary).
- Use caution with analgesics (opioids) and antidiarrheal medications.
- Steroid* refractory (if not responsive within 24–72 hours to high-dose IV steroid* infusion)
  - ☐ Infliximab (Remicade®) 5 mg/kg infusion may be considered.
  - ☐ May require one or more infusions to manage symptoms (may readminister at weeks 2 and 6)
  - ☐ Avoid with bowel perforation or sepsis.
  - ☐ 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 for at least four weeks
  - ☐ Supportive medications for symptomatic management
    - Loperamide 2 capsules at the onset and 1 with each diarrhea stool thereafter, with maximum of 6 tablets per day
    - Diphenoxylate and atropine, 1–4 tablets per day; simethicone when necessary

Continued on the next page

APPENDIX B. *(CONTINUED)*

CARE STEP PATHWAY FOR MANAGEMENT OF GASTROINTESTINAL TOXICITY: DIARRHEA AND COLITIS

NURSING IMPLEMENTATION

- Compare baseline assessment; grade and document bowel frequency.
- Early identification and evaluation of patient symptoms
- Grade symptom, and determine level of care and interventions required.
- Early intervention with laboratory work and office visit if colitis symptoms are suspected

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

- Taper should consider patient's current symptom profile.
- Close follow-up in person or by telephone, based on individual need and symptomatology
- Anti-acid therapy daily as gastric ulcer prevention while on steroids
- Review steroid medication side effects: mood changes (anger, reactive, hyperaware, euphoric, mania); increased appetite; interrupted sleep; oral thrush; fluid retention)
- Be alert to recurring symptoms as steroids taper down and report them (taper may need to be adjusted).

Long-term high-dose steroids

- Consider antimicrobial prophylaxis (sulfamethoxazole and trimethoprim double dose Monday, Wednesday, and Friday; single dose if used daily) or alternative if sulfa-allergic (e.g., atovaquone [Mepron®] 1,500 mg by mouth daily)
- Consider additional antiviral and antifungal coverage.
- Avoid alcohol and acetaminophen, as well as 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

Note. Based on information from Bristol-Myers Squibb, 2017a, 2017b; Champiat et al., 2016; Dadu et al., 2016; Fecher et al., 2013; Kähler et al., 2016; Kumar et al., 2017; Merck, 2017; Naidoo et al., 2015; National Cancer Institute, 2010; Spain et al., 2016; U.S. Food and Drug Administration, 2012; Weber et al., 2016.

APPENDIX C.

CARE STEP PATHWAY FOR MANAGEMENT OF MUCOSITIS AND 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 any of the following?
  - ☐ Mouth pain (tongue, gums, buccal mucosa)
  - ☐ Mouth sores
  - ☐ Difficulty eating
  - ☐ Waking during sleep to sip water
  - ☐ Recent dental-related issues
  - ☐ Dental work need (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

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)

GRADING TOXICITY: XEROSTOMIA (DRY MOUTH)

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 of more than 0.2 ml per minute

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 flow of 0.1–0.2 ml per minute with oral intake

Grade 3 (severe)

- Inability to adequately aliment orally; tube feeding or total parenteral nutrition indicated; unstimulated saliva of less than 0.1 ml per minute

Grade 4 (potentially life-threatening)

- Life-threatening consequences; urgent intervention indicated

Grade 5 (death)

MANAGEMENT

Overall strategy

- Assess for other etiology of mucositis or dry mouth: candidiasis; ask patient about new medications (particularly antihistamines), including herbals, supplements, and alternative and complementary therapies.

Intervention (at-risk patients)

- Advise basic oral hygiene.
  - ☐ Tooth brushing (soft toothbrush, avoid toothpaste with whitening agents)
  - ☐ Use of dental floss daily
  - ☐ More than one mouth rinse per day to maintain oral hygiene (avoid commercial mouthwashes or those with alcohol)
- If patient wears dentures, assess for proper fit and areas of irritation.
- Dental referral if necessary
- Assess patient and family understanding of prevention strategies and rationale.
  - ☐ Identify barriers to adherence.

Continued on the next page

APPENDIX C. *(CONTINUED)*

CARE STEP PATHWAY FOR MANAGEMENT OF MUCOSITIS AND XEROSTOMIA

MANAGEMENT BY GRADE

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 hydrochloride
- Assess patient and family understanding of recommendations and rationale.
  - ☐ Identify barriers to adherence.

Grade 2 (moderate)

- Ipilimumab to be withheld for any grade 2 event (resume when grade 0 or 1)
- Immunotherapy to be discontinued for grade 2 events persisting six or more weeks (ipilimumab) or 12 or more weeks (pembrolizumab, nivolumab)
- Assess for Sicca syndrome and Sjögren syndrome.
- Encourage vigilant oral hygiene.
- Xerostomia
  - ☐ Advise moistening agents (saliva substitute, synthetic saliva, oral lubricants).
  - ☐ Advise secretagogues, both nonpharmacologic (sugarless gum and hard candies, natural lemon) and pharmacologic (pilocarpine, cevimeline hydrochloride).
- Mucositis
  - ☐ Vigilant oral hygiene
    - Increase frequency of brushing to every four 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® and Zilactin®; 2% viscous lidocaine applied to lesions 15 minutes prior to meals; 2% morphine mouthwash; 0.5% doxepin mouthwash; "miracle mouthwash" of diphenhydramine, lidocaine, and simethicone)
    - Corticosteroid rinses (dexamethasone oral solution)
  - ☐ Monitor weight and hydration status.
  - ☐ Nutrition referral, if appropriate
  - ☐ Assess patient and family understanding of toxicity and rationale for interventions, as well as treatment hold.
    - Identify barriers to adherence.

Grades 3–4 (severe or life-threatening)

- Nivolumab to be withheld for first occurrence of grade 3 event; immunotherapy to be discontinued for any grade 4 event or for a grade 3 event persisting 12 or more 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 and family understanding of toxicity and rationale for interventions, as well as treatment discontinuation.
  - ☐ Identify barriers to adherence.

Note. Based on information from Bristol-Myers Squibb, 2017a, 2017b; Dadu et al., 2016; Friedman et al., 2016; Lalla et al., 2014; Merck, 2017; National Cancer Institute, 2010; Van Sebille et al., 2015.

APPENDIX D.

CARE STEP PATHWAY FOR MANAGEMENT OF 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 or tea-colored)?
- Abdominal pain, specifically in the right upper quadrant?
- Bruising or bleeding more easily?
- Fevers?
- Change in mental status?
- Increased sweating?

Recognize

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

GRADING TOXICITY: ULN

Grade 1 (mild)

- AST/ALT: Greater than ULN, less than or equal to 3 times ULN
- Bilirubin: Greater than ULN, less than or equal to 1.5 times ULN

Grade 2 (moderate)

- AST/ALT: Greater than 3 times ULN, less than or equal to 5 times ULN
- Bilirubin: Greater than 1.5 times ULN, less than or equal to 3 times ULN

Grade 3 (severe)

- AST/ALT: Greater than 5 times ULN, less than or equal to 20 times ULN
- Bilirubin: Greater than 3 times ULN

Grade 4 (potentially life-threatening)

- AST/ALT: Greater than 20 times ULN
- Bilirubin: Greater than 10 times ULN

Grade 5 (death)

MANAGEMENT

Overall strategy

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

Continued on the next page

APPENDIX D. *(CONTINUED)*

CARE STEP PATHWAY FOR MANAGEMENT OF HEPATOTOXICITY: IMMUNOTHERAPY-INDUCED INFLAMMATION OF LIVER TISSUE

MANAGEMENT BY GRADE

Grade 1 (mild)

- Immunotherapy may be withheld if LFTs are trending upward; recheck LFTs within approximately one week.

Grade 2 (moderate)

- Immunotherapy to be withheld; recheck LFTs daily for three days or every three days; resume when complete or partial resolution of adverse reaction (grade 0 or 1).
- Immunotherapy to be discontinued for grade 2 events lasting six or more weeks (ipilimumab) or 12 or more weeks (pembrolizumab, nivolumab), or for inability to reduce steroid dose to 7.5 mg prednisone or equivalent per day
- Consider starting steroids* 0.5–1 mg/kg prednisone or equivalent per day (IV methylprednisolone 125 mg total daily dose) and an anti-acid.
- Consider hospital admission for IV steroids*.
- If LFTs are normalized and symptoms resolved, steroids* to be tapered for four or more weeks when function recovers
- Once patient returns to baseline or grades 0–1, consider resuming treatment.

Grade 3 (severe)

- Steroids* to be initiated at 2 mg/kg prednisone or equivalent daily (oral).
- Nivolumab to be withheld for first occurrence of 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 or more weeks
- Admission for IV steroids*
- Rule out 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
  - ☐ Mycophenolate mofetil (CellCept®) 500–1,000 mg by mouth every 12 hours, or
  - ☐ Antithymocyte globulin infusion (Atgam®, Thymoglobulin®)
- Hepatology and gastroenterology consultation
- Consider liver biopsy.
- If LFTs are stable or declining daily for five consecutive days, decrease LFT checks to every three days, then weekly.
  - ☐ If LFTs are normalized and symptoms resolved, steroids* to be tapered for four or more weeks

Grade 4 (life-threatening)

- Immunotherapy to be discontinued
- Hospital admission
- Steroids* to be initiated at 2 mg/kg prednisone or equivalent daily via IV
- Rule out hepatitis infection.
- Daily LFTs
- If sustained elevation and refractory to steroids*, potential for adding to steroid regimen
  - ☐ Mycophenolate mofetil 500–1,000 mg by mouth every 12 hours, or
  - ☐ Antithymocyte globulin infusion
- Hepatology or gastroenterology consultation
- Consider liver biopsy.
- If LFTs are stable or declining daily for five consecutive days, decrease LFT checks to every three days, then weekly.
- If LFTs are normalized and symptoms resolved, steroids* to be tapered slowly for four or more weeks.

NURSING IMPLEMENTATION

- Review LFT results prior to administration of immunotherapy.
- Early identification and evaluation of patient symptoms
- Early intervention with laboratory work and office visit if hepatotoxicity is suspected
- Grade LFT results and any other accompanying symptoms.

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

- Taper should consider patient's current symptom profile.
- Close follow-up in person or by telephone, based on individual need and symptomatology
- Anti-acid therapy daily as gastric ulcer prevention while on steroids
- Review steroid medication side effects: mood changes (anger, reactive, hyperaware, euphoric, mania); increased appetite; interrupted sleep; oral thrush; fluid retention)
- Be alert to recurring symptoms as steroids taper down and report them (taper may need to be adjusted).

Long-term high-dose steroids

- Consider antimicrobial prophylaxis (sulfamethoxazole and trimethoprim double dose Monday, Wednesday, and Friday; single dose if used daily) or alternative if sulfa-allergic (e.g., atovaquone [Mepron®] 1,500 mg by mouth daily)
- Consider additional antiviral and antifungal coverage.
- Avoid alcohol and acetaminophen, as well as other hepatoxins.

RED FLAGS

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

ALT—alanine aminotransferase; AST—aspartate aminotransferase; LFT—liver function test; SGOT—serum glutamic oxaloacetic transaminase; SGPT—serum glutamic pyruvic transaminase; ULN—upper limit of normal

Note. Based on information from Bristol-Myers Squibb, 2017a, 2017b; Champiat et al., 2016; Dadu et al., 2016; Fecher et al., 2013; Friedman et al., 2016; Kähler et al., 2016; Kumar et al., 2017; Merck, 2017; Naidoo et al., 2015; Spain et al., 2016; U.S. Food and Drug Administration, 2012; Weber et al., 2016.

APPENDIX E.

CARE STEP PATHWAY FOR MANAGEMENT OF HYPOPHYSITIS: INFLAMMATION OF 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 the following:
  - ☐ Change in energy?
  - ☐ Headache?
  - ☐ Dizziness?
  - ☐ Nausea or 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 ADLs (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 six or more weeks or for inability to reduce steroid dose to 7.5 mg or less prednisone or equivalent per day
- Nivolumab to be withheld for grade 2 or 3 hypophysitis and discontinued for grade 4 hypophysitis; pembrolizumab to be withheld for grade 2 hypophysitis and withheld or discontinued for grade 3 or 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 and slowly taper over at least four weeks*
- Long-term supplementation of affected hormones is often required.
  - ☐ Secondary hypothyroidism requiring levothyroxine replacement
  - ☐ Secondary hypoadrenalism requiring replacement hydrocortisone (typical dose of 20 mg in the am and 10 mg in the pm)
- Assess risk of opportunistic infection based on duration of steroid taper (and consider antimicrobial 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 brain MRI is ordered with pituitary cuts or via pituitary protocol.
- Anticipate treatment with corticosteroid and immunotherapy hold.
- Review proper administration of corticosteroid.
  - ☐ Take with food.
  - ☐ Take in am.
- Educate patient regarding possibility of permanent loss of organ function (pituitary and possibly others if involved, including thyroid and adrenal glands).
- Sick-day instructions and vaccinations

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

- Taper should consider patient's current symptom profile.
- Close follow-up in person or by telephone, based on individual need and symptomatology
- Anti-acid therapy daily as gastric ulcer prevention while on steroids
- Review steroid medication side effects: mood changes (anger, reactive, hyperaware, euphoric, mania); increased appetite; interrupted sleep; oral thrush; fluid retention)
- Be alert to recurring symptoms as steroids taper down and report them (taper may need to be adjusted).
- Avoid alcohol and acetaminophen, as well as other hepatoxins.

Long-term high-dose steroids

- Consider antimicrobial prophylaxis (sulfamethoxazole and trimethoprim double dose Monday, Wednesday, and Friday; single dose if used daily) or alternative if sulfa-allergic (e.g., atovaquone [Mepron®] 1,500 mg by mouth daily)
- Consider additional antiviral and antifungal coverage.
- Avoid alcohol and acetaminophen, as well as other hepatoxins.

RED FLAGS

- Symptoms of adrenal insufficiency

ACTH—adrenocorticotropic hormone; ADLs—activities of daily living; DDX—differential diagnosis; FSH—follicule-stimulating hormone; GH—growth hormone; LH—luteinizing hormone; MRI—magnetic resonance imaging; TSH—thyroid stimulating hormone

Note. Based on information from Bristol-Myers Squibb, 2017a, 2017b; Byun et al., 2017; Champiat et al., 2016; Dadu et al., 2016; Fecher et al., 2013; Friedman et al., 2016; Kähler et al., 2016; Kumar et al., 2017; Merck, 2017; Naidoo et al., 2015; National Cancer Institute, 2010; U.S. Food and Drug Administration, 2012; Weber et al., 2016.

APPENDIX F.

CARE STEP PATHWAY FOR MANAGEMENT OF THYROIDITIS: INFLAMMATION OF THYROID GLAND

NURSING ASSESSMENT

Look

- Does the patient appear unwell?
- Changes in weight since last visit?
- Changes in hair texture or thickness?
- Appearing hot or cold?
- Does the patient look fatigued?

Listen

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

Recognize

- Ensure that patient undergoes TFTs prior to first dose, every 12 weeks while on PD-1 therapy, and every three weeks with ipilimumab
- High TSH with low free T4 consistent with primary hypothyroidism
- DDX: secondary hypothyroidism because of 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 (less than 0.01 mIU/L) with normal or high free T3 or T4

- Acute thyroiditis
- Rarely Graves'-like disease

TSH greater than 5 and less than 10 mIU/L with normal free T4 or T3

- Subclinical hypothyroidism

TSH greater than 10 mIU/L with normal or low free T4 and T3

- Primary hyperthyroidism

TSH low (less than 0.01 mIU/L) with high free T4 or T3

- Hyperthyroidism

MANAGEMENT BY GRADE

TSH low (less than 0.01 mIU/L) with normal or high free T3 or T4

- Consider measuring antithyroid antibodies and/or TSH-receptor autoantibodies to establish autoimmune etiology.
- If patient has not received IV iodinated contrast within two months, can consider a diagnostic thyroid uptake and scan
- Acute thyroiditis usually resolves or progresses to hypothyroidism; consequently, can repeat TFTs in four to six weeks
- If TSH-receptor antibodies high, obtain a thyroid uptake scan and refer to endocrinology.
- Short period of 1 mg/kg prednisone or equivalent per day may be helpful in acute thyroiditis.
- Consider use of beta blockers and immunotherapy hold for symptomatic patients (e.g., beta blockers for tachycardia or murmur and immunotherapy holds for patients who have acute thyroiditis threatening an airway). Therapy is often restarted when symptoms are mild or tolerable.

TSH greater than 5 and less than 10 mIU/L with normal free T4 or T3

- Repeat TFTs in four to six weeks.

TSH greater than 10 mIU/L with normal or low free T4 and T3

- Begin thyroid replacement if symptomatic.
- May consider repeating levels in two to four weeks if asymptomatic
- Levothyroxine dose 1.6 mcg per weight (kg) or 75–100 mcg daily
- Repeat TSH in four to six weeks, and titrate dose to reference range TSH.

TSH low (less than 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, particularly if the patient is hyperthyroid and 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

Note. Based on information from Bristol-Myers Squibb, 2017a, 2017b; Champiat et al., 2016; Dadu et al., 2016; Fecher et al., 2013; Friedman et al., 2016; Kähler et al., 2016; Kumar et al., 2017; Merck, 2017; Naidoo et al., 2015; National Cancer Institute, 2010; U.S. Food and Drug Administration, 2012; Weber et al., 2016.

APPENDIX G.

CARE STEP PATHWAY FOR MANAGEMENT OF 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 patient's breath have a sweet or fruity smell?
- Is the patient tachycardic?

Listen

- Frequent urination?
- Increased thirst?
- Increased hunger?
- Increased fatigue?
- Altered level of consciousness may occur 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 greater than ULN, less than or equal to 160 mg/dl

Grade 2 (moderate)

- Fasting glucose value greater than 160 mg/dl, less than or equal to 250 mg/dl

Grade 3 (severe)

- Fasting glucose value greater than 250 mg/dl, less than or equal to 500 mg/dl; hospitalization indicated

Grade 4 (potentially life-threatening)

- Fasting glucose value greater than 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 consultation

NURSING IMPLEMENTATION

- Discuss that type 1 diabetes mellitus will likely be permanent.
- Review signs and symptoms of hyperglycemia and hypoglycemia.
- Follow patients closely with checks on blood glucose levels, fruity breath, and other symptoms (e.g., increased infections).
- Ensure early intervention.
- Provide insulin education (or refer).
- Discuss possibility of other immune-related adverse events, including others of endocrine origin.

ULN—upper limit of normal

Note. Based on information from Bristol-Myers Squibb, 2017a, 2017b; Merck, 2017; National Cancer Institute, 2010; U.S. Food and Drug Administration, 2012.

APPENDIX H.

CARE STEP PATHWAY FOR MANAGEMENT OF PNEUMONITIS: INFLAMMATION OF LUNG ALVEOLI

NURSING ASSESSMENT

Look

- Does the patient appear uncomfortable?
- Did the patient have difficulty walking to the examination 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 to last visit? Is it low on exertion?
- Is there a preexisting pulmonary autoimmune condition (e.g., sarcoidosis)?
- Is there a history of prior respiratory compromise (e.g., asthma, chronic obstructive pulmonary disease, congestive heart failure)?
- Has the patient experienced other immune-related adverse events?

GRADING TOXICITY: PNEUMONITIS

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)	

GRADING TOXICITY: HYPOXIA

A disorder characterized by a 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 (pulse oximetry of less than 88%); intermittent supplemental oxygen	■ Decreased oxygen saturation at rest (pulse oximetry of less than 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, and lung disease.
- Early intervention to maintain or improve physical function and impact on quality of life
- Assess pulse oximetry (resting and on exertion) at baseline and at each visit to assist in identifying a decrease at early onset.

Prevention

- No known interventions

Continued on the next page

APPENDIX H. *(CONTINUED)*

CARE STEP PATHWAY FOR MANAGEMENT OF PNEUMONITIS: INFLAMMATION OF LUNG ALVEOLI

MANAGEMENT BY GRADE

Grade 1 (mild)

- Anticipate immunotherapy to continue.
- Continue to monitor via radiology testing (every two to four 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 or 1)
- Immunotherapy to be discontinued for recurrent (pembrolizumab, nivolumab) or persistent (ipilimumab, pembrolizumab, nivolumab) grade 2 events
- Anticipate treatment with
  - ☐ Corticosteroids (e.g., prednisone or equivalent 1–2 mg/kg per day) until symptoms improve to baseline, then slow taper for at least one 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 and family understanding of recommendations and rationale.
  - ☐ Identify barriers to adherence.

Grades 3–4 (severe or life-threatening)

- Discontinue immunotherapy for grade 3 or 4 events.
- Patient will likely need to be admitted to hospital for further management and supportive care.
- Anticipate the use of high-dose IV corticosteroids (e.g., methylprednisolone or equivalent 2–4 mg/kg per day).
- Once symptoms have resolved to baseline or grade 1, convert to equivalent oral corticosteroid dose, then taper slowly for at least one 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 and family understanding of toxicity and rationale for treatment discontinuation.
  - ☐ Identify barriers to adherence, specifically compliance with medication and physical activity.

NURSING IMPLEMENTATION

- Identify high-risk individuals (e.g., asthma, chronic obstructive pulmonary disease) 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 per day) and that the patient will be on corticosteroid therapy for at least one 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
- The risk of pneumonitis is greater in patients receiving combination immunotherapy regimens.

ADLs—activities of daily living

Note. Based on information from Bristol-Myers Squibb, 2017a, 2017b; Dadu et al., 2016; Fecher et al., 2013; Friedman et al., 2016; Kähler et al., 2016; Kumar et al., 2017; Merck, 2017; Naidoo et al., 2015; National Cancer Institute, 2010; Spain et al., 2016; U.S. Food and Drug Administration, 2012; Weber et al., 2016.

APPENDIX I.

CARE STEP PATHWAY FOR MANAGEMENT OF ARTHRALGIAS AND ARTHRITIS

NURSING ASSESSMENT

Look

- Does the patient appear uncomfortable?
- Does the patient appear unwell?
- Is the patient's 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 falling? Other safety issues?
- Associated symptoms?
  - ☐ Fatigue (new or worsening)

Recognize

- Is there a preexisting autoimmune dysfunction?
- Is there a history of prior orthopedic injury, degenerative joint disease, osteoarthritis, or rheumatoid arthritis?
- Other immune-related adverse effects
- Three subtypes of inflammatory arthritis associated with checkpoint inhibitors
  - ☐ Polyarthritis, similar to rheumatoid arthritis
  - ☐ True reactive arthritis with conjunctivitis, urethritis, and oligoarthritis
  - ☐ Subtype similar to seronegative spondyloarthritis with inflammatory back pain and predominantly larger joint involvement

GRADING TOXICITY: ARTHRALGIA

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 ADLs	■ Severe pain; limiting self-care ADLs		

GRADING TOXICITY: ARTHRITIS

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 ADLs	■ Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self-care ADLs		

MANAGEMENT

Overall strategy

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

Prevention

- No known interventions

Continued on the next page

APPENDIX I. *(CONTINUED)*

CARE STEP PATHWAY FOR MANAGEMENT OF ARTHRALGIAS AND ARTHRITIS

MANAGEMENT BY GRADE

Grade 1 (mild)

- Anticipate immunotherapy to continue.
- Encourage physical activity.
  - ☐ 30 minutes of low- to moderate-intensity physical activity five days per week can improve physical conditioning and sleep and decrease pain perception.
  - ☐ For physically inactive patients, advise supervised exercise and resistance training.
  - ☐ Other options: yoga, tai chi, Qigong, Pilates, aquatic exercise, focused dance program
- Anticipate use of analgesia.
  - ☐ Low-dose NSAIDs, topical (diclofenac gel or patch; for localized, limited, superficial joint inflammation or patients who cannot tolerate oral NSAIDs) and oral (ibuprofen, naproxen, celecoxib); provide guidance on proper administration.
- Assess patient and family understanding of recommendations and rationale.
  - ☐ Identify barriers to adherence.

If symptoms do not improve in four to six weeks, escalate to the next level of therapy.

Grade 2 (moderate)

- Ipilimumab to be withheld for any grade 2 event (until grade 0 or 1) and discontinued for events persisting six or more weeks or inability to reduce steroid dose to 7.5 mg prednisone or equivalent per day
- Dose of pembrolizumab or nivolumab to be held to avoid making symptoms worse
- Pembrolizumab or nivolumab to be discontinued for grade 2 events persisting 12 or more weeks
- Continue to encourage physical activity.
- Anticipate use of analgesia.
  - ☐ NSAIDs (oral NSAIDs include ibuprofen, naproxen, celecoxib); provide anticipatory guidance on proper administration.
- Anticipate referral to rheumatology for collaborative management and consideration of adjunct treatment.
- Anticipate previsit assessment: complete blood count, erythrocyte sedimentation rate, C-reactive protein, blood urea nitrogen/creatinine and aminotransferases, antinuclear antibody, rheumatoid factor

Grade 2 *(continued)*

- ☐ Intraarticular steroids to be used for significant symptomatic joint(s)
- ☐ Low-dose corticosteroids (0.5 – 1 mg/kg per day) to be used (anticipatory guidance should be provided on proper administration; duration of corticosteroid therapy is usually limited, lasting about four to six weeks, with possible resolution of symptoms within weeks to months of treatment)
- Assess patient and family understanding of toxicity and rationale for treatment hold (if applicable).
  - ☐ Identify barriers to adherence.

If symptoms do not improve in four to six weeks, escalate to the next level of therapy.

Grades 3–4 (severe or life-threatening)

- Pembrolizumab or nivolumab to be withheld for first occurrence of grade 3 or 4 event and discontinued if the following occur:
  - ☐ Grade 3 or 4 event recurs
  - ☐ Persists 12 or more weeks
- Ipilimumab to be discontinued for any grade 3 or 4 event
- High-dose steroids (1–1.5 mg/kg per day in divided doses)
  - ☐ Anticipatory guidance on proper administration should be provided.
  - ☐ Onset of action is rapid (typically within days)
- Anticipate referral to rheumatology for collaborative management and consideration of adjunct treatment.
  - ☐ Nonbiologic agents are more likely to be recommended; conventional synthetic DMARDs, which have a delayed effect and take weeks to work, include methotrexate, sulfasalazine, hydroxychloroquine, and leflunomide.

Grades 3–4 *(continued)*

- ☐ Biologic agents are less likely to be recommended; they include biologic DMARDs, tumor necrosis factor inhibitors (infliximab, etanercept, adalimumab, golimumab, certolizumab pegol), and anti B-cell agents, which are CD-20 blocking (rituximab).
- ☐ Agents not advised include the following: interleukin-6 receptor blocking agent (tocilizumab) and Janus kinase inhibitors (tofacitinib) because of risk of colonic perforation; T-cell co-stimulation inhibitor (abatacept) because it directly opposes the mechanism of checkpoint blockade agents
- Assess patient and family understanding of toxicity and rationale for treatment discontinuation.
  - ☐ Identify barriers to adherence, specifically compliance with medication and 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 immune-related adverse events with checkpoint inhibitors.
- Arthritis-like symptoms can range from mild, which are managed well with NSAIDs and low-dose corticosteroids, to severe and erosive, which require multiple immunosuppressant medications.
- Anticipate that the steroid requirements to manage arthralgias can be much higher (as much as 1.5 mg/kg per 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 because of mobility issue

ADLs—activities of daily living; DMARD—disease-modifying antirheumatic drug; NSAID—nonsteroidal anti-inflammatory drug
Note. Based on information from Bristol-Myers Squibb, 2017a, 2017b; Cappelli, Naidoo, et al., 2017; Cappelli, Shah, et al., 2017; Durham et al., 2015; Merck, 2017; National Cancer Institute, 2010.

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APPENDIX J.

CARE STEP PATHWAY FOR MANAGEMENT OF 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, any respiratory difficulties?

Listen

- Reported weakness (unilateral or bilateral)?
- Reported new or worsened pain, numbness, or tingling?
- Reported 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 symptoms?
- Results of prior imaging
  - ☐ Metastases to spinal cord
  - ☐ Other metastases that may cause symptoms

GRADING TOXICITY: 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
- Life-threatening; urgent intervention indicated

Grade 5 (death)

MANAGEMENT

Overall strategy

- Rule out infectious, noninfectious, and disease-related etiologies.
- High-dose steroids (1-2 mg/kg prednisone or equivalent per day in divided doses) 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 six or more weeks or inability to reduce steroid dose to 7.5 mg or less prednisone or equivalent per day; pembrolizumab or nivolumab to be discontinued for grade 3 or 4 events that recur or persist 12 or more weeks, or inability to reduce steroid dose to 10 mg or less prednisone or equivalent per day
- Neurology consultation
  - ☐ Consideration of electromyelogram and nerve conduction tests
  - ☐ Immune globulin infusions
  - ☐ Plasmapheresis
- Taper steroids slowly for at least four weeks once symptoms improve.
- If needed, obtain physical therapy or occupational therapy consult (for functional assessment and to evaluate safety of patient at home).
- Supportive medications for symptomatic management

NURSING IMPLEMENTATION

- Compare baseline assessment; grade and document neuropathy and etiology (diabetic, medication, vascular, chemotherapy).
- Early identification and evaluation of patient symptoms
- Early intervention with laboratory work and office visit if neuropathy symptoms suspected
- Steroid taper instructions and calendar as a guide but not an absolute
  - ☐ Taper should consider patient's current symptom profile.
  - ☐ Close follow-up in person or by telephone, based on individual need and symptomatology
  - ☐ Anti-acid therapy daily as gastric ulcer prevention while on steroids
  - ☐ Review steroid medication side effects: mood changes (anger, reactive, hyperaware, euphoric, mania); increased appetite; interrupted sleep; oral thrush; fluid retention)
  - ☐ Be alert to recurring symptoms as steroids taper down and report them (taper may need to be adjusted).
- Long-term high-dose steroids
  - ☐ Consider antimicrobial prophylaxis for pneumocystis pneumonia.
  - ☐ Consider additional antiviral and antifungal coverage.

RED FLAGS

- Guillain-Barré syndrome
- Myasthenia gravis

ADLs—activities of daily living

Note. Based on information from Bristol-Myers Squibb, 2017a, 2017b; Kumar et al., 2017; Merck, 2017; National Cancer Institute, 2010; Spain et al., 2016.

APPENDIX K.

CARE STEP PATHWAY FOR MANAGEMENT OF 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 the following?
  - ☐ Urinary tract infection
  - ☐ Pyelonephritis
  - ☐ Worsening congestive heart failure
- Are symptoms limiting ADLs?
- Current or recent use of nephrotoxic medications (prescribed and over-the-counter) and other agents?
  - ☐ NSAIDs
  - ☐ Antibiotics
  - ☐ Contrast media or other nephrotoxic agents (contrast dye, aminoglycosides, proton pump inhibitor)?

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

A disorder characterized by the acute loss of renal function that is traditionally classified as prerenal, renal, and postrenal

Grade 1 (mild)

- Creatinine level greater than 0.3 mg/dl; creatinine greater than 1.5 times ULN but less than or equal to 2 times ULN

Grade 2 (moderate)

- Creatinine greater than 2 times and less than or equal to 3 times ULN

Grade 3 (severe)

- Creatinine greater than 3 times ULN or greater than 4 mg/dl; hospitalization indicated

Grade 4 (potentially life-threatening)

- Life-threatening consequences; dialysis indicated

Grade 5 (death)

MANAGEMENT

Overall strategy

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

ADLs—activities of daily living; NSAID—nonsteroidal anti-inflammatory drug; PD-1—programmed cell death protein 1; ULN—upper limit of normal

Note. Based on information from Bristol-Myers Squibb, 2017a, 2017b; Kähler et al., 2016; Kumar et al., 2017; Merck, 2017; National Cancer Institute, 2010; Rassy et al., 2016; Spain et al., 2016.

MANAGEMENT BY GRADE

Mild elevation in creatinine (grade 1)

- Anticipate immunotherapy to continue.
- Perform detailed review of concomitant medications (prescribed and over-the-counter), including herbals and vitamins, anticipating possible discontinuation of nephrotoxic agents.
- Avoid or minimize addition of nephrotoxic agents, such as contrast media for radiology tests.
- Anticipate close monitoring of creatinine (weekly).
- Educate patient and 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 or 1 and discontinued for events persisting six or more weeks or inability to reduce steroid dose to 7.5 mg prednisone per day)
- Pembrolizumab or nivolumab to be withheld for grade 2 events persisting 12 or more weeks or inability to reduce steroid dose to 10 mg or less prednisone or equivalent per day
- Anticipate increase in frequency of creatinine monitoring (every two to three days until improvement).
- Immunosuppressive medications to be initiated to treat immune-mediated nephritis
  - ☐ Systemic corticosteroids (e.g., prednisone) 0.5–1 mg/kg per day until symptoms improve to baseline, followed by slow taper for at least one month
  - ☐ Anticipate increase in corticosteroid dosing (treat as if grade 3 nephritis) if creatinine does not improve within 48–72 hours.
  - ☐ Anticipate use of additional supportive care medications.
- On symptom resolution to patient baseline or grade 1, begin to taper corticosteroid dose slowly for one month.
- Anticipatory guidance on proper administration
- Anticipate the use of IV fluid to ensure hydration.
- Anticipate that nephrology consultation may be initiated by the provider.
- Assess patient and 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 of grade 3 or 4 event and discontinued if the following occur:
  - ☐ Grade 3 or 4 event recurs
  - ☐ Persists for 12 or more weeks
  - ☐ Requires more than 10 mg prednisone or equivalent per day for more than 12 weeks
- Ipilimumab to be discontinued for any grade 3 or 4 event
- Immunosuppressive medications to be initiated to treat immune-mediated nephritis
  - ☐ Corticosteroids (e.g., prednisone 1–2 mg/kg per day in divided doses) until symptoms improve to baseline, then slow taper for at least one month
  - ☐ If symptoms do not improve within 48–72 hours, additional immunosuppressive medications will be considered.
- Anticipate that nephrology consultation will be initiated by the 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 preexisting 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 that the steroid requirements to manage immune-mediated nephritis are high (as much as 1–2 mg/kg per day) and that patients will be on corticosteroid therapy for at least one 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
- The 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.