

BC Cancer Protocol Summary for Management of Immune-Mediated Adverse Reactions to Checkpoint Inhibitor Immunotherapy

Protocol Code	SCIMMUNE
Tumour Group	Supportive Care
Contact Physician	Dr. Kerry Savage

Eligibility

Patients treated with immunotherapy agents with checkpoint inhibition, including:

- CTLA-4 inhibitors (e.g., ipilimumab, [tremelimumab](#))
- PD-1 inhibitors (e.g., nivolumab, pembrolizumab, [dostarlimab](#))
- PD-L1 inhibitors (e.g., atezolizumab, avelumab, durvalumab)

These agents are associated with immune-mediated adverse reactions, although the incidence may vary from agent to agent. **Reactions can be severe to fatal** and usually occur during the treatment course. They may include enterocolitis, intestinal perforation or hemorrhage, hepatitis, dermatitis, neuropathy, endocrinopathy, as well as toxicities in other organ systems. Early diagnosis and appropriate management are essential to minimize life-threatening complications. For specific toxicity management, see the following flow diagrams.

Infusion-related reactions

Isolated cases of severe reactions have been reported. In the case of a severe reaction, infusion of the checkpoint inhibitor(s) should be discontinued and appropriate medical therapy administered. Patients with a mild or moderate infusion reaction may receive checkpoint inhibitors with close monitoring. Premedication with acetaminophen and an antihistamine may be considered.

Potential immune-mediated adverse reactions include, but are not limited to:

If severe or clinically significant:

- **Discontinue the checkpoint inhibitor(s)**
 - prednISONE 1 to 2 mg/kg/day PO or methylPREDNISolone 1 to 2 mg/kg/day IV
 - Corticosteroid eye drops for uveitis, iritis or episcleritis
 - Consider referring to a specialist
1. **Blood and lymphatic:** hemolytic anemia, immune thrombocytopenic purpura, hypereosinophilia
 2. **Cardiovascular:** angiopathy, myositis, myocarditis, pericarditis, temporal arteritis, vasculitis
 3. **Endocrine:** primary and secondary hypothyroidism, hyperthyroidism, autoimmune thyroiditis (with hyperthyroidism followed by hypothyroidism), hyperglycemia (with diabetic ketoacidosis), hypopituitarism, primary and secondary adrenal insufficiency, hypoparathyroidism
 4. **Eye:** blepharitis, conjunctivitis, episcleritis, iritis, scleritis, uveitis
 5. **Gastrointestinal:** gastritis, colitis
 6. **Pancrease/liver:** pancreatitis, hepatitis
 7. **Musculoskeletal:** arthritis, polymyalgia rheumatica
 8. **Skin:** rash, eczema, psoriasis, Stevens-Johnson Syndrome, leukocytoclastic vasculitis
 9. **Neurologic:** peripheral neuropathy, Guillan-Barré Syndrome, myasthenia gravis, meningitis
 10. **Lung:** pneumonitis, bronchiolitis obliterans organizing pneumonia

Dosing of PD-1/PD-L1 checkpoint inhibitors and immune-related adverse events⁸⁻¹²

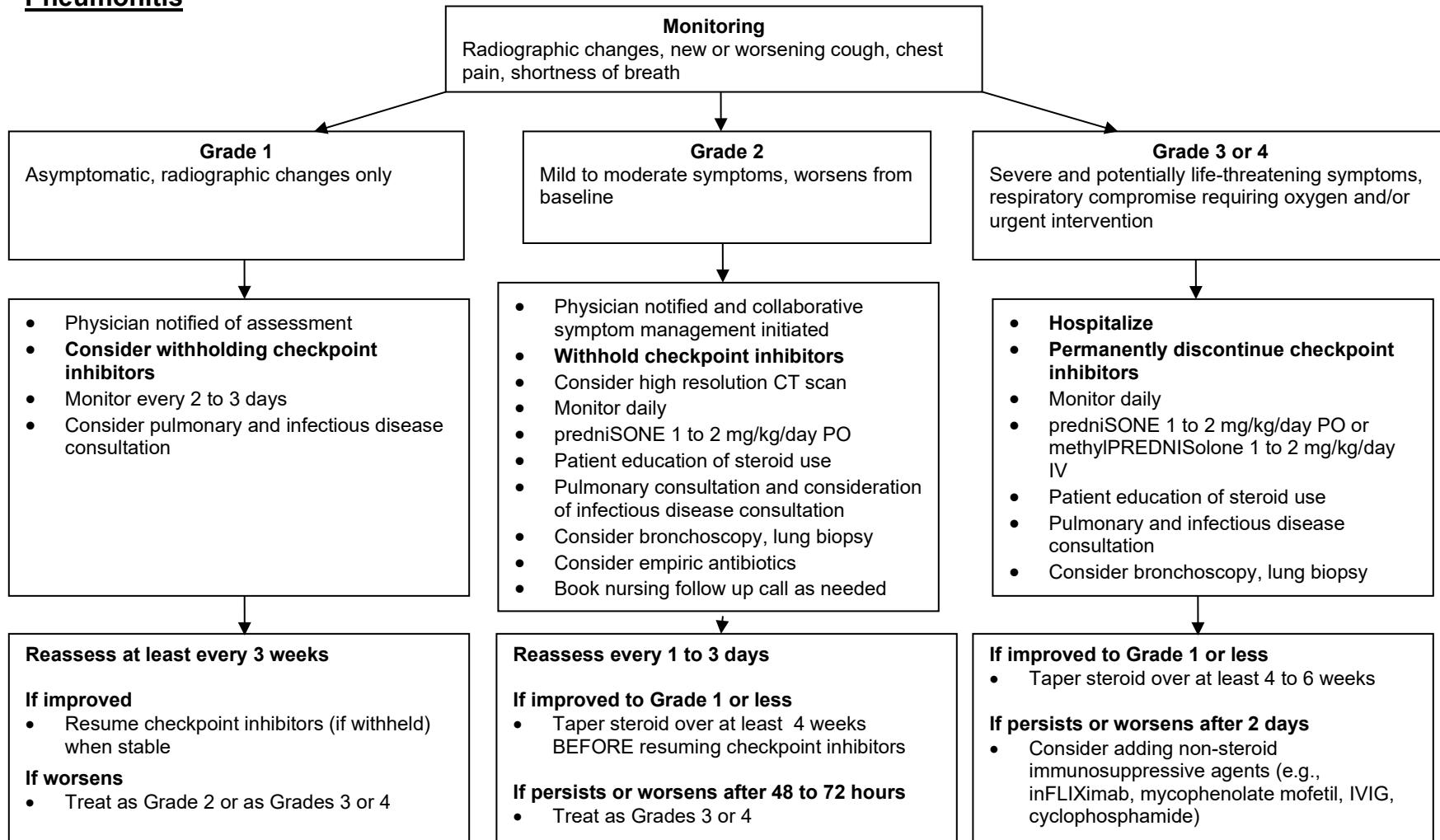
- Both standard and extended dosing regimens have similar pharmacokinetics and appear to have similar efficacy and safety
- Incidence of immune-related adverse effects does not appear to increase with increased doses used in extended interval dosing
- Extended dosing regimens reduce the number of clinic visits, thereby:
 - Decreasing workload within the healthcare system
 - Decreasing travel burden for patients
 - Reducing potential infectious disease exposure by limiting the physical interaction between staff and patients
- See Systemic Therapy Update, Dec 2020, for further details

References:

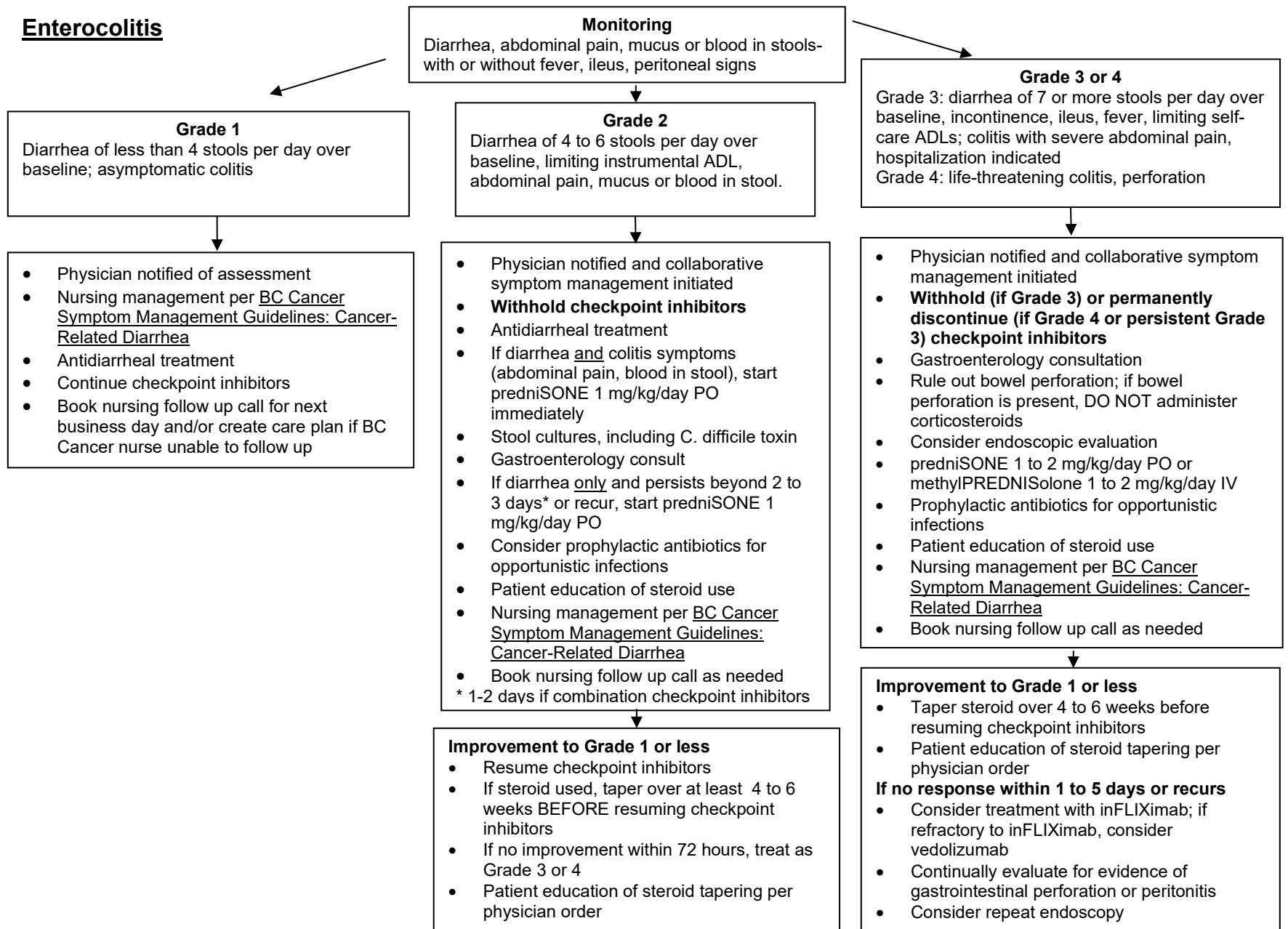
1. Larkin J, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med* 2015;373:23-34.
2. Bristol-Myers Squibb Pharma: YERVOY (ipilimumab) summary of product characteristics. Uxbridge, United Kingdom: 2 July 2012.
3. Bristol-Myers Squibb: YERVOY (ipilimumab): Serious and fatal immune-mediated adverse reactions - YERVOY Risk Evaluation and Mitigation Strategy (REMS). <http://www.yervoy.com/hcp/rems.aspx> (Accessed in October, 2012)
4. Momtaz P, Park V, Panageas KS, et al. Safety of infusing ipilimumab over 30 minutes. *J Clin Oncol* (ePub 29 June 2015).
5. Bristol-Myers Squibb: OPDIVO (nivolumab) product monograph. Montreal, Quebec: 26 October 2016.
6. Bristol-Myers Squibb: OPDIVO prescribing information. Princeton, NJ: November 2016.
7. Weber JS, et al. Management of adverse events following treatment with anti-programmed death-1 agents. *Oncologist* 2016;21:1-11.
8. Zhao X, Shen J, Ivaturi V, et al. Model-based evaluation of the efficacy and safety of nivolumab once every 4 weeks across multiple tumor types. *Ann Oncol* 2020;31(2):302-9.
9. Lala M, Li TR, de Alwis DP, et al. A six-weekly dosing schedule for pembrolizumab in patients with cancer based on evaluation using modeling and simulation. *Eur J Cancer* 2020;131:68-75.
10. Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum–etoposide versus platinum–etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. *Lancet* 2019; 394: 1929–39.
11. Rizvi NA, Cho BC, Reinmuth N, et al. Durvalumab with or without tremelimumab vs standard chemotherapy in first-line treatment of metastatic non-small cell lung cancer: the MYSTIC phase 3 randomized clinical trial. *JAMA Oncol* 2020;6(5):661-74.
12. Morrissey KM, Marchand M, Patel H, et al. Alternative dosing regimens for atezolizumab: an example of model informed drug development in the postmarketing setting. *Cancer Chemother Pharmacol* 2019; 84:1257-67.
13. Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 2018;36(17):1714-1768.
14. Cancer Care Ontario. Immune checkpoint inhibitor toxicity management – clinical practice guideline. March 23, 2018.
15. Haanen JBAG, Carbonnel F, Robert C, et al. Management of toxicities from immunotherapy: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Annals of Oncol* 2017;28(Supplement 4):i119-i142.
16. National Comprehensive Cancer Network. Management of immunotherapy of immunotherapy-related toxicities. Version 1.2020 – December 16, 2019.
17. Puzanov I, Diab A, Abdallah K, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer* 2017;5:95-123.
18. U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. November 27, 2017.
19. National Comprehensive Cancer Network. Management of immunotherapy of immunotherapy-related toxicities. Version 4.2021 – September 27, 2021.
20. AstraZeneca Canada Inc. IMJUDO® product monograph. Mississauga, Ontario; May 13, 2024.
21. GlaxoSmithKline Inc. JEMPERLI® product monograph. Mississauga, Ontario; July 23, 2024.

For grading details, see: [Grading System of Immune-Related Adverse Events Associated with Checkpoint Immunotherapy](#), below chart

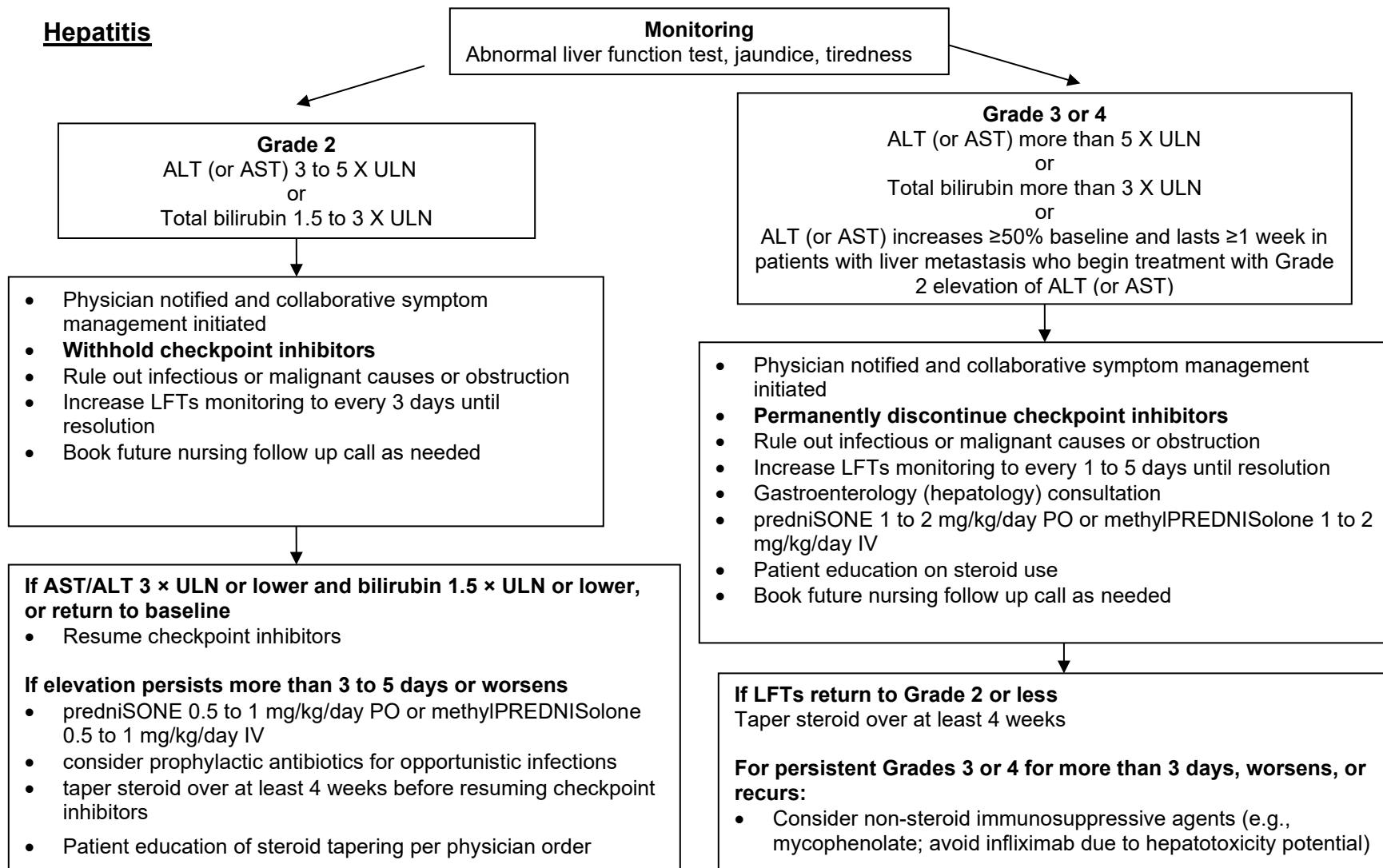
Pneumonitis



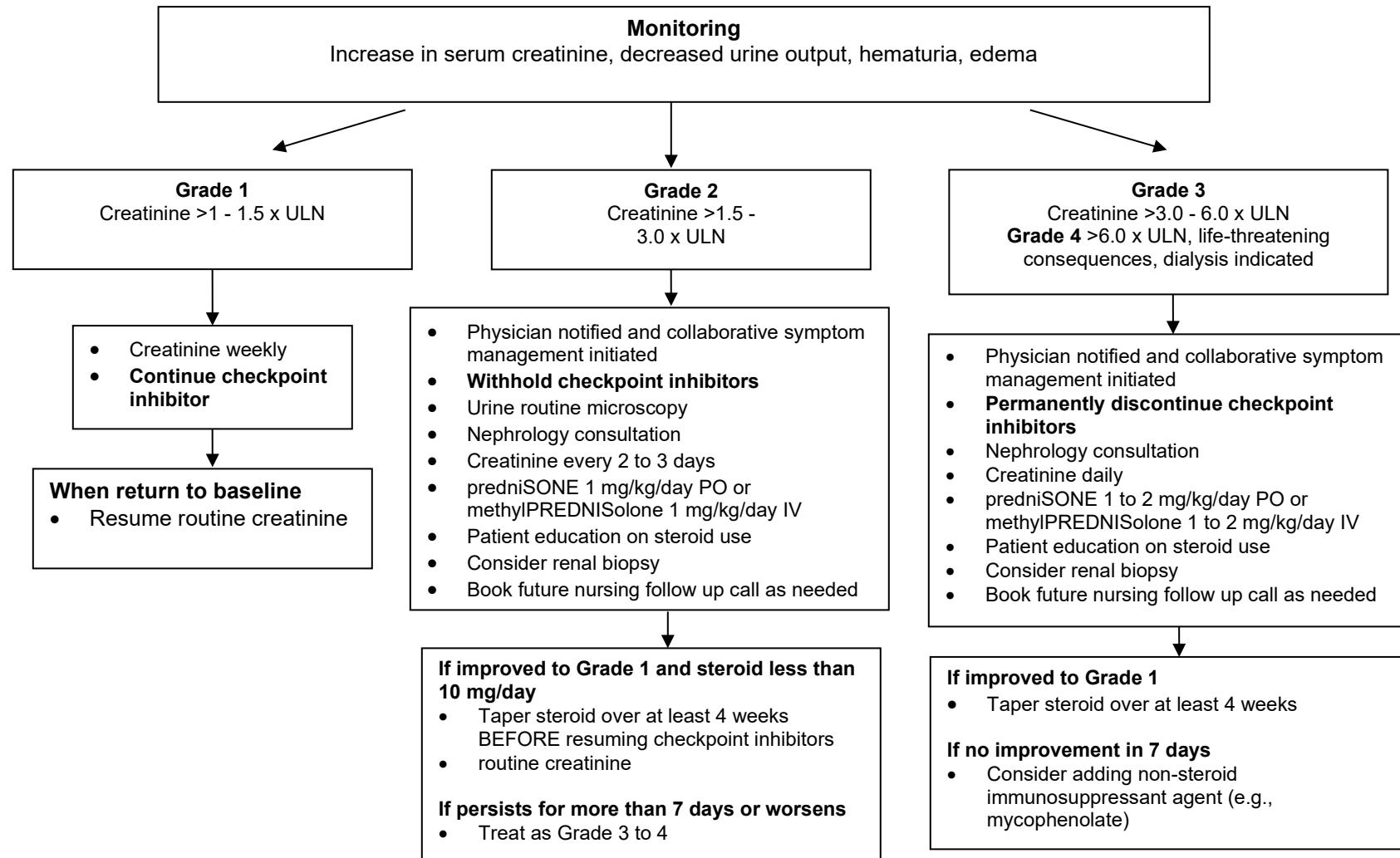
Enterocolitis



Hepatitis



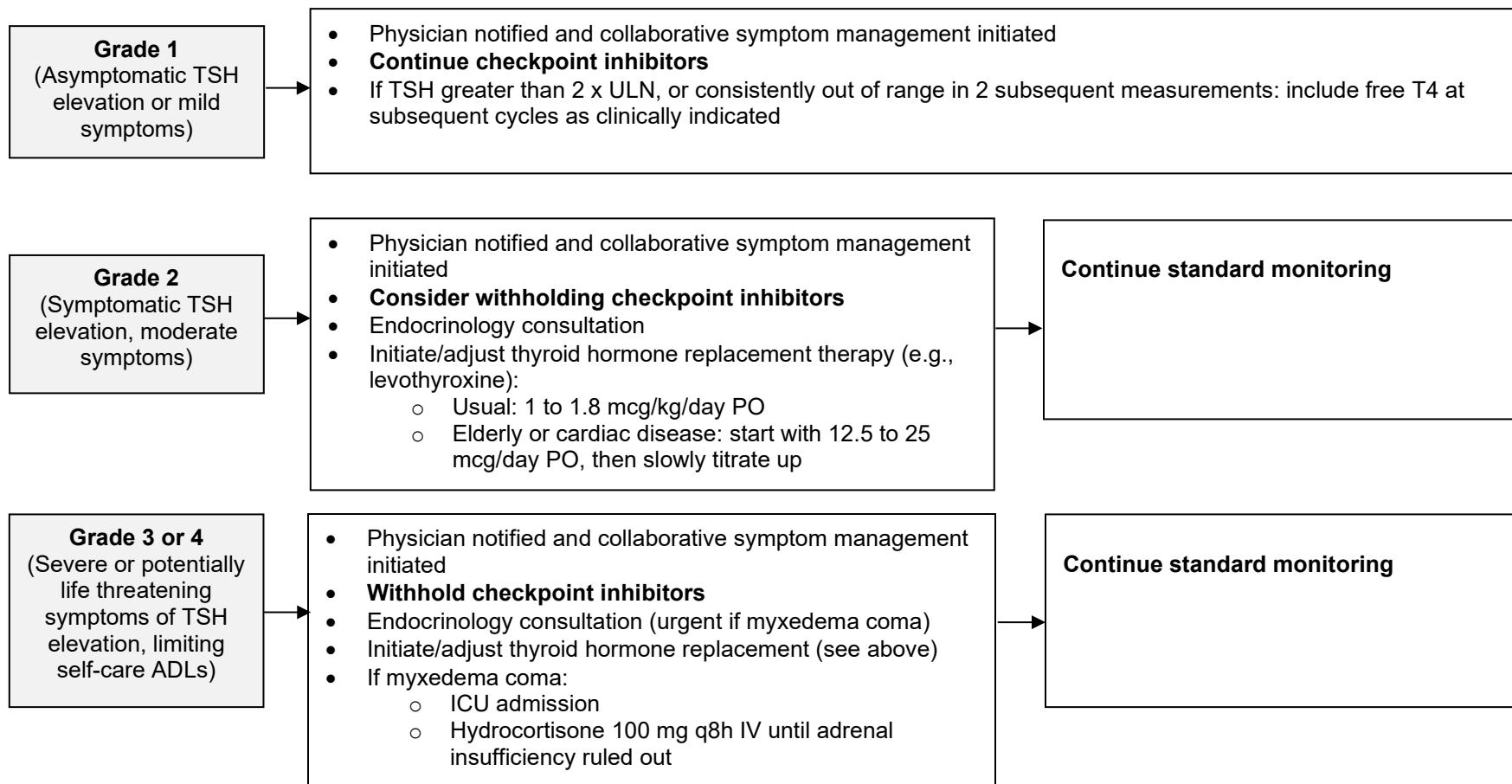
Nephritis



Endocrine: Hypothyroidism

Monitoring

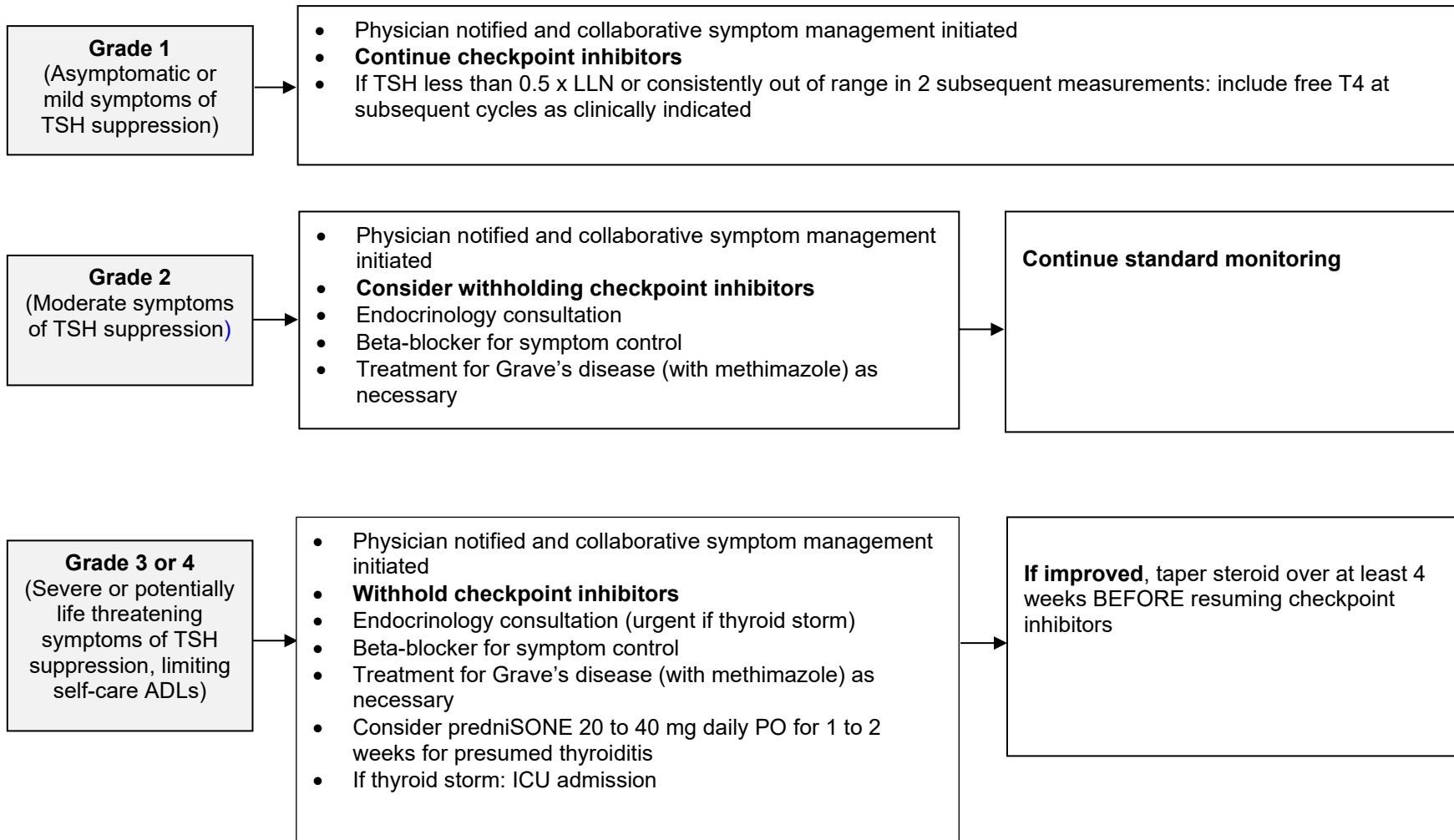
Extreme tiredness, weight gain, mood or behaviour changes (e.g., decreased libido, confusion, forgetfulness), dizziness or fainting, hair loss, feeling cold, constipation, hoarseness



Endocrine: Hyperthyroidism

Monitoring

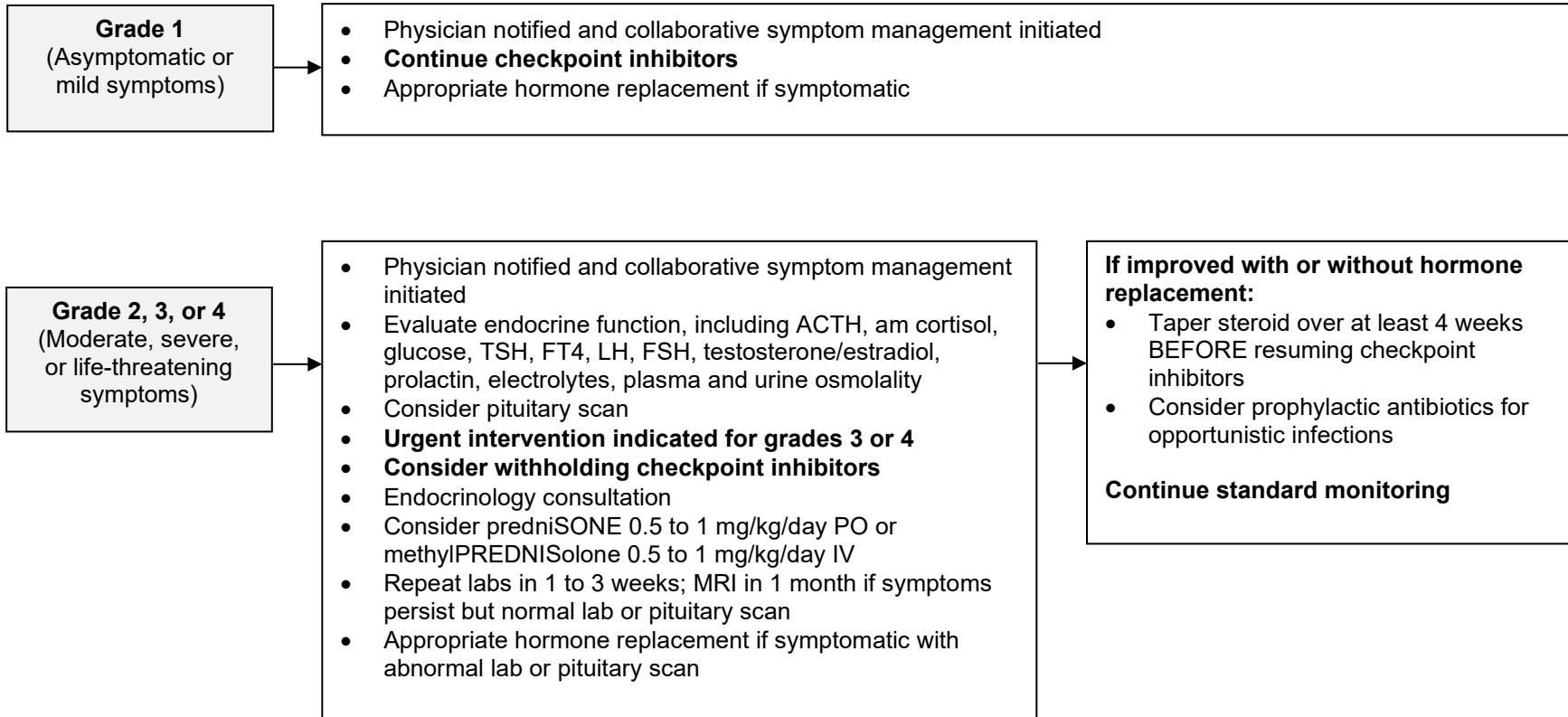
Weight loss, increased frequency of bowel movements, heat intolerance, sweating, tremor, palpitations, anxiety, fatigue, goiter



Endocrine: Hypophysitis

Monitoring

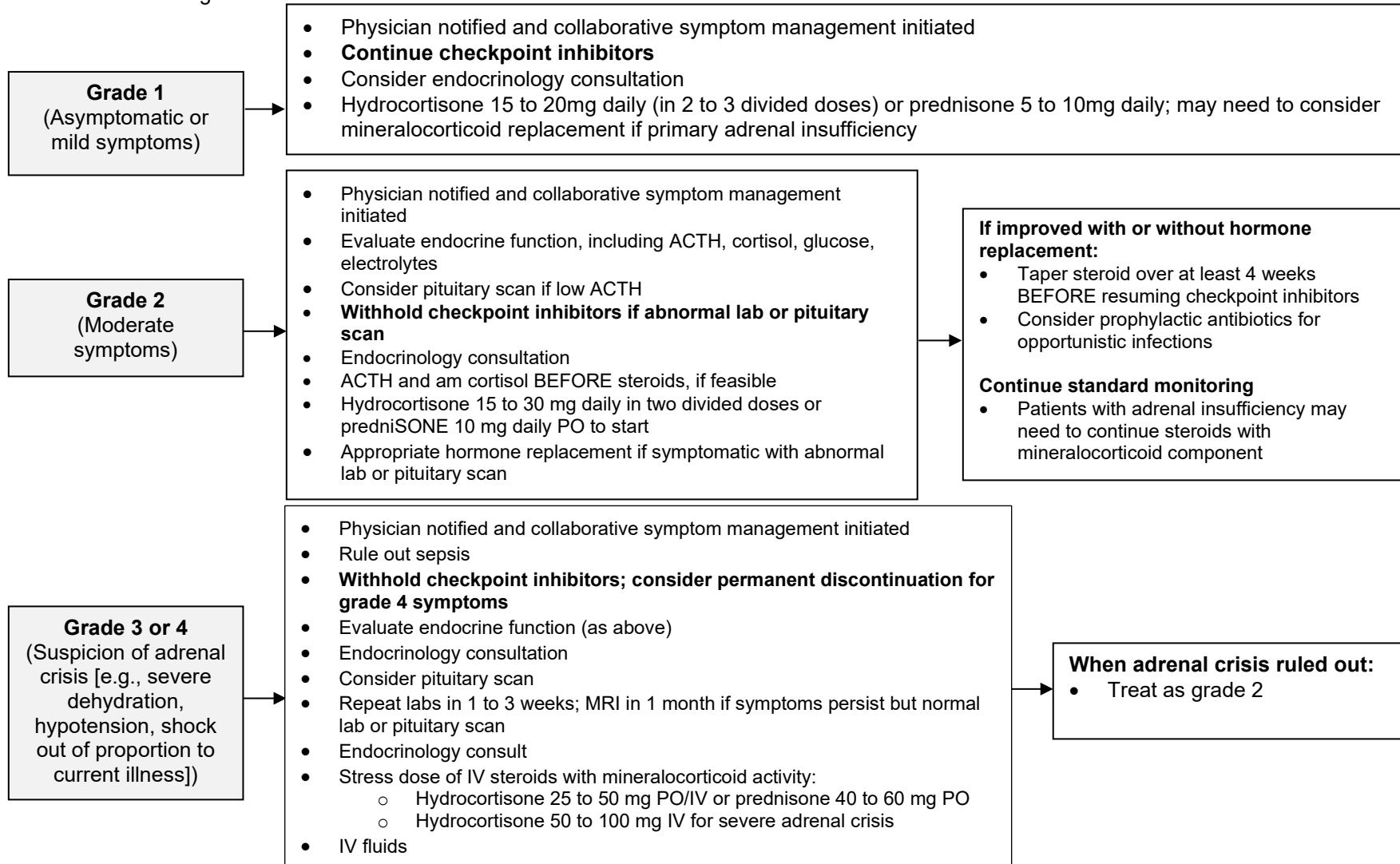
Persistent or unusual headaches, vision changes, extreme tiredness, weight gain or loss, mood or behaviour changes (e.g., decreased libido, confusion, forgetfulness), dizziness or fainting, hair loss, feeling cold, constipation, hoarseness



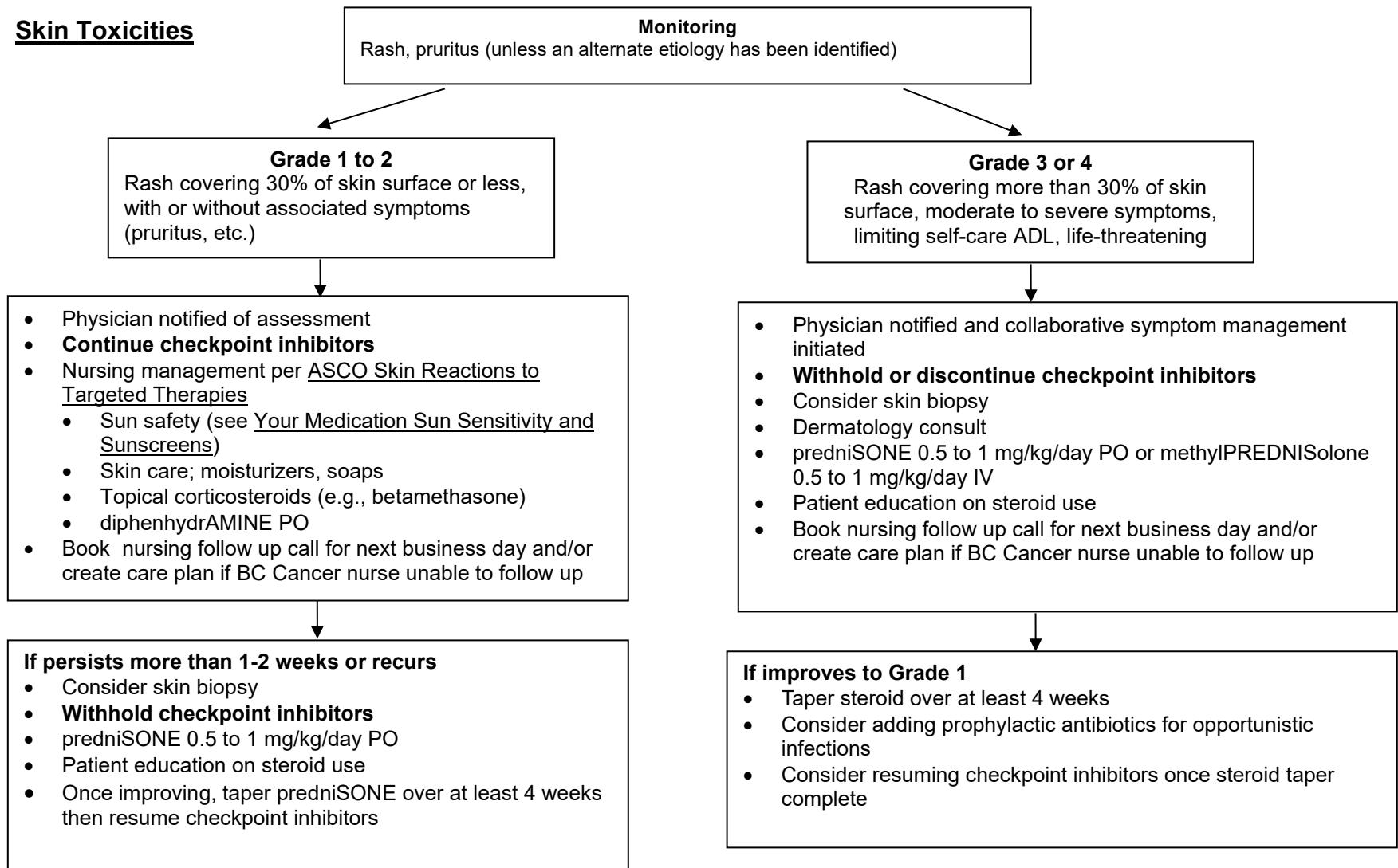
Endocrine: Adrenal Insufficiency

Monitoring

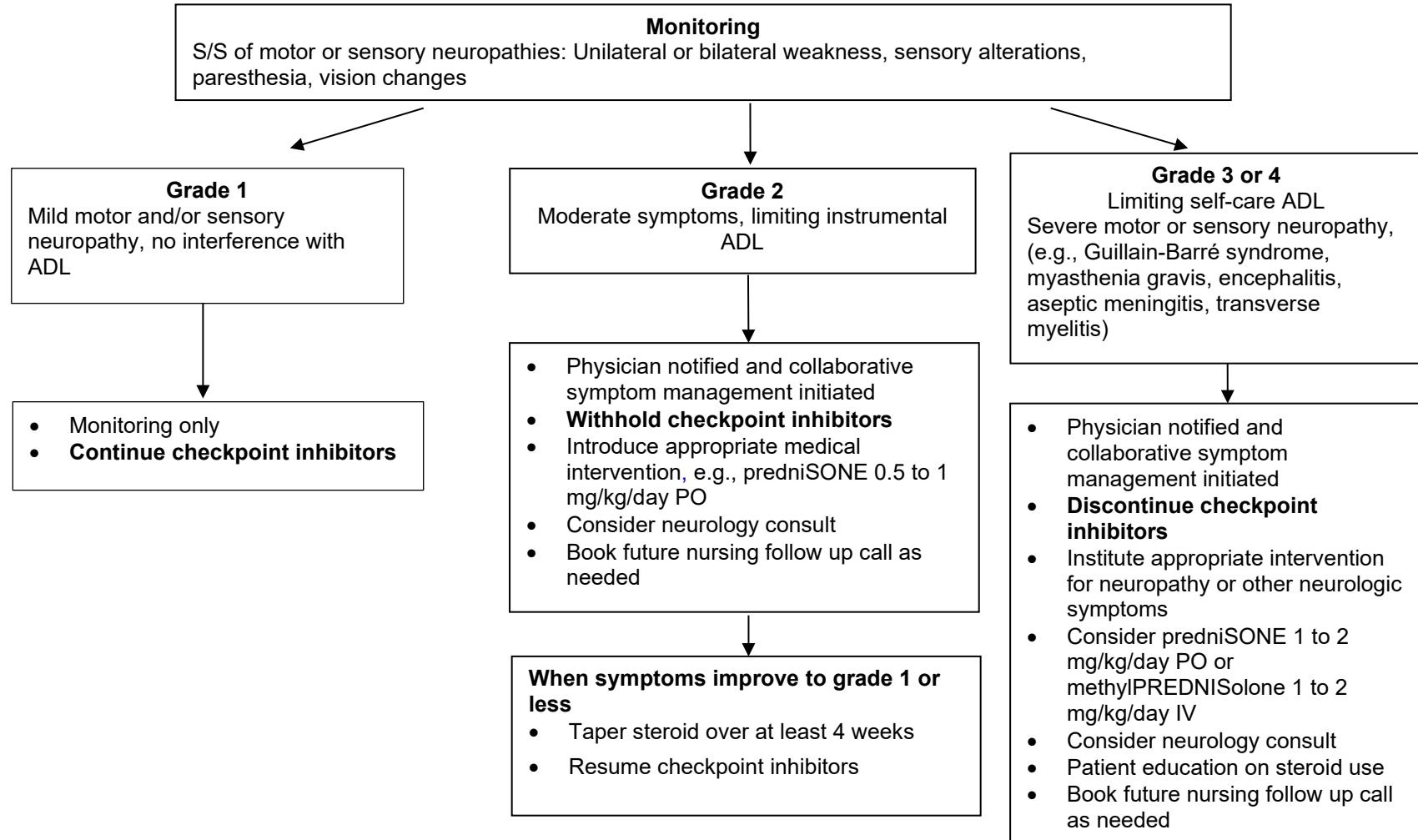
Persistent or unusual headaches, extreme tiredness, weakness, dehydration, mood or behaviour changes (e.g., confusion, forgetfulness), dizziness or fainting



Skin Toxicities



Neurologic Toxicities



Grading System of Immune-Related Adverse Events Associated with Checkpoint Immunotherapy

Immune-Related Adverse Events	Grade 1	Grade 2	Grade 3	Grade 4
Pneumonitis	Asymptomatic, radiographic changes only	Mild to moderate symptoms, worsens from baseline	Severe symptoms, respiratory compromise requiring oxygen	Potentially life-threatening symptoms, respiratory compromise requiring oxygen and/or urgent intervention
Enterocolitis	Diarrhea of less than 4 stools per day over baseline; asymptomatic colitis	Diarrhea of 4 to 6 stools per day over baseline, limiting instrumental ADL, abdominal pain, mucus or blood in stool.	Diarrhea of 7 or more stools per day over baseline, incontinence, ileus, fever, limiting self-care ADLs; colitis with severe abdominal pain, hospitalization indicated	life-threatening colitis, perforation
Hepatitis		ALT (or AST) 3 to 5 X ULN or Total bilirubin 1.5 to 3 X ULN	ALT (or AST) more than 5 X ULN or Total bilirubin more than 3 X ULN	ALT (or AST) increases ≥50% baseline and lasts ≥1 week in patients with liver metastasis who begin treatment with Grade 2 elevation of ALT (or AST)
Nephritis	Creatinine >1 - 1.5 x ULN	Creatinine >1.5 - 3.0 x ULN	Creatinine >3.0 - 6.0 x ULN	Creatinine >6.0 x ULN, life-threatening consequences, dialysis indicated
Hypothyroidism	Asymptomatic TSH elevation or mild symptoms	Symptomatic TSH elevation, moderate symptoms	Severe symptoms of TSH elevation	Potentially life threatening symptoms of TSH elevation
Hyperthyroidism	Asymptomatic or mild symptoms of TSH suppression	Moderate symptoms of TSH suppression	Severe symptoms of TSH suppression	Potentially life threatening symptoms of TSH suppression
Hypophysitis	Asymptomatic or mild symptoms	Moderate symptoms	Severe symptoms	Life-threatening symptoms
Adrenal Insufficiency	Asymptomatic or mild symptoms	Moderate symptoms	Suspicion of adrenal crisis (e.g., severe dehydration, hypotension, shock out of proportion to current illness)	

Immune-Related Adverse Events	Grade 1	Grade 2	Grade 3	Grade 4
Skin Toxicities	Rash covering 30% of skin surface or less, with or without associated symptoms (pruritus, etc.)		Rash covering more than 30% of skin surface, moderate to severe symptoms, limiting self-care ADL, life-threatening	
Neurologic Toxicities	Mild motor and/or sensory neuropathy, no interference with ADL	Moderate symptoms, limiting instrumental ADL	Limiting self-care ADL Severe motor or sensory neuropathy, (e.g., Guillain-Barré syndrome, myasthenia gravis, encephalitis, aseptic meningitis, transverse myelitis)	