

# 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. **Pancreas/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 events<sup>8-12</sup>

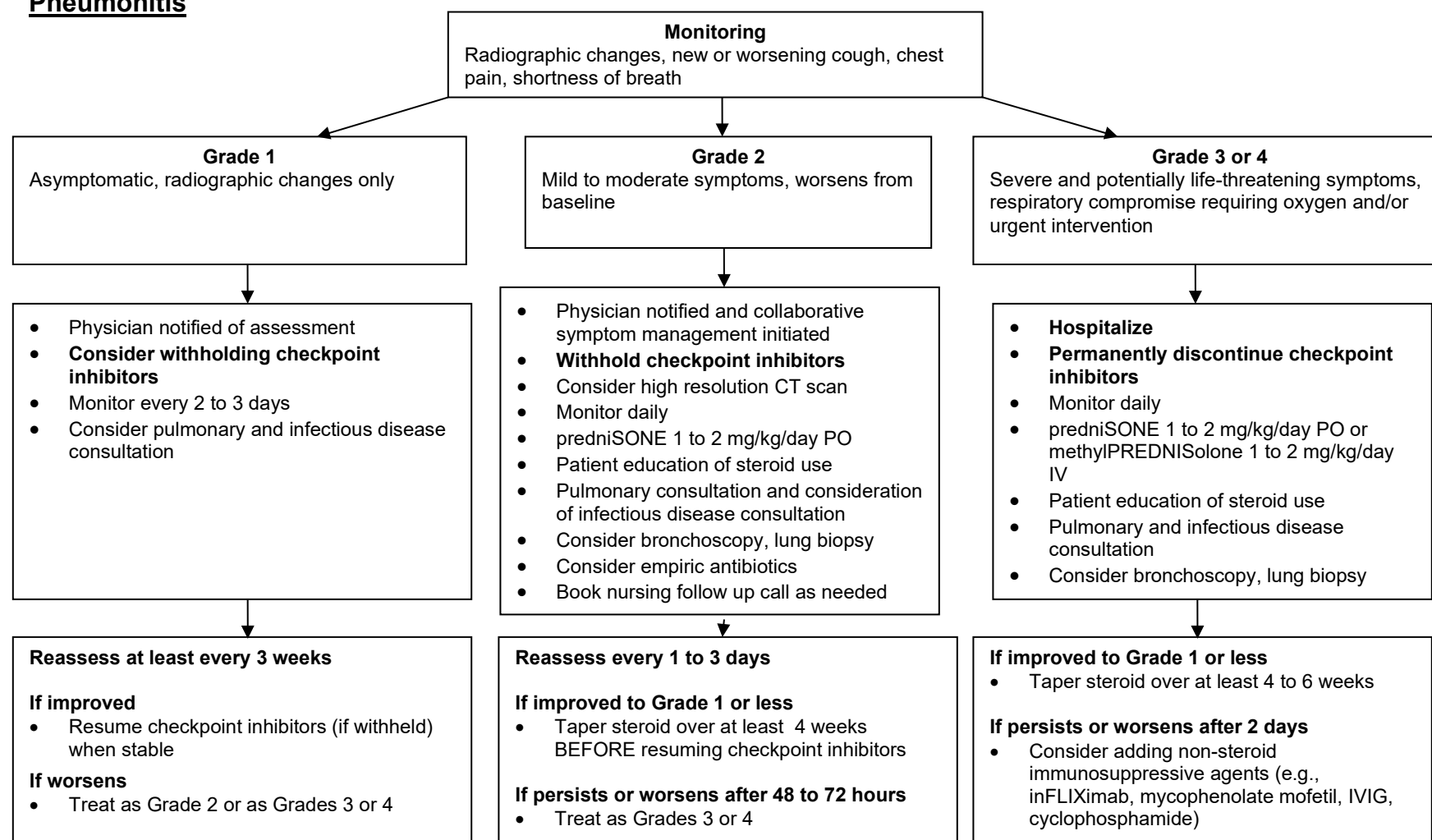
- Both standard and extended dosing regimens have similar pharmacokinetics and appear to have similar efficacy and safety
- Incidence of immune-related adverse effects does not appear to increase with increased doses used in extended interval dosing
- Extended dosing regimens reduce the number of clinic 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:

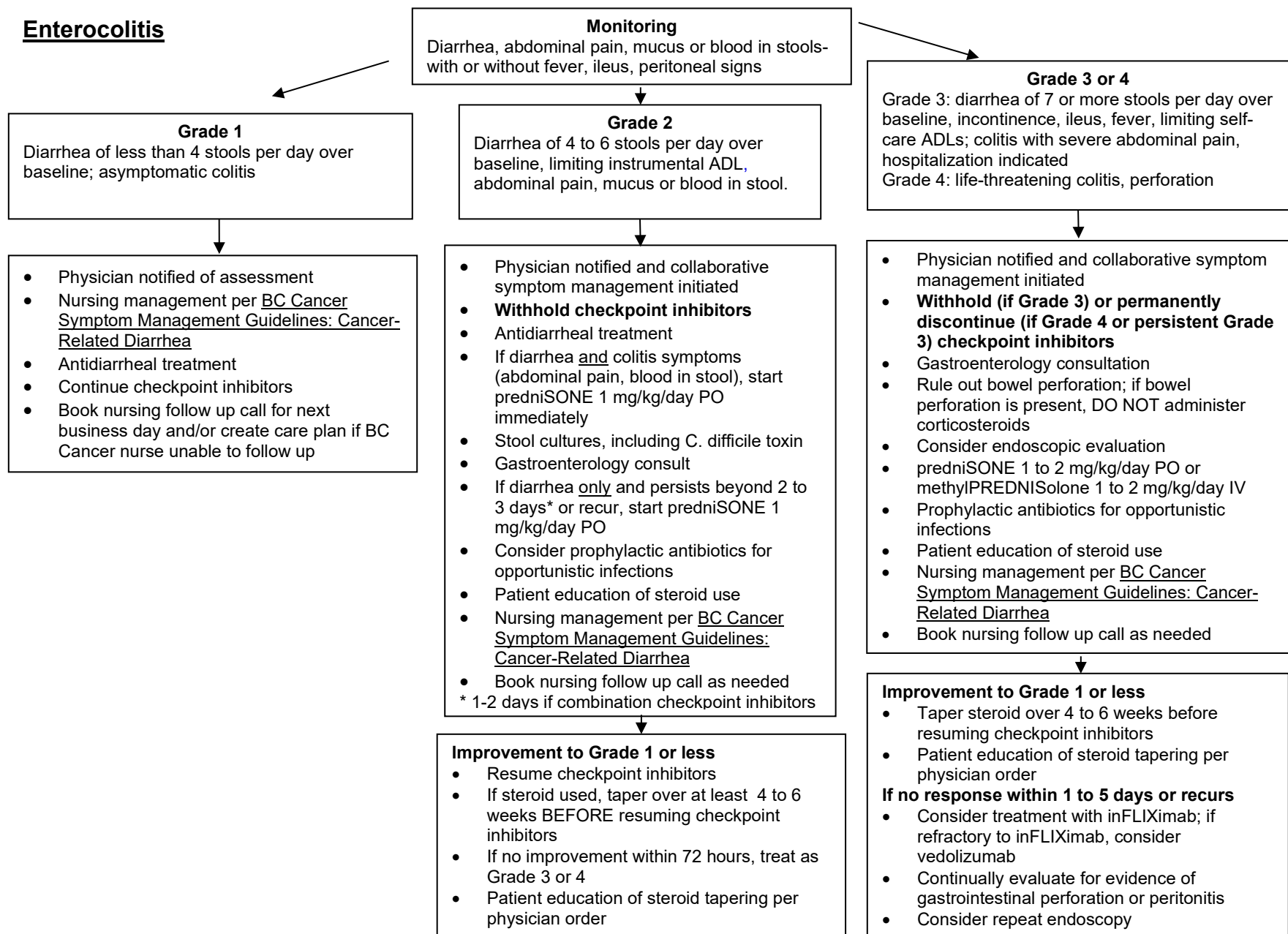
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2. Bristol-Myers Squibb Pharma: YERVOY (ipilimumab) summary of product characteristics. Uxbridge, United Kingdom: 2 July 2012.
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For grading details, see: [Grading System of Immune-Related Adverse Events Associated with Checkpoint Immunotherapy](#), below chart

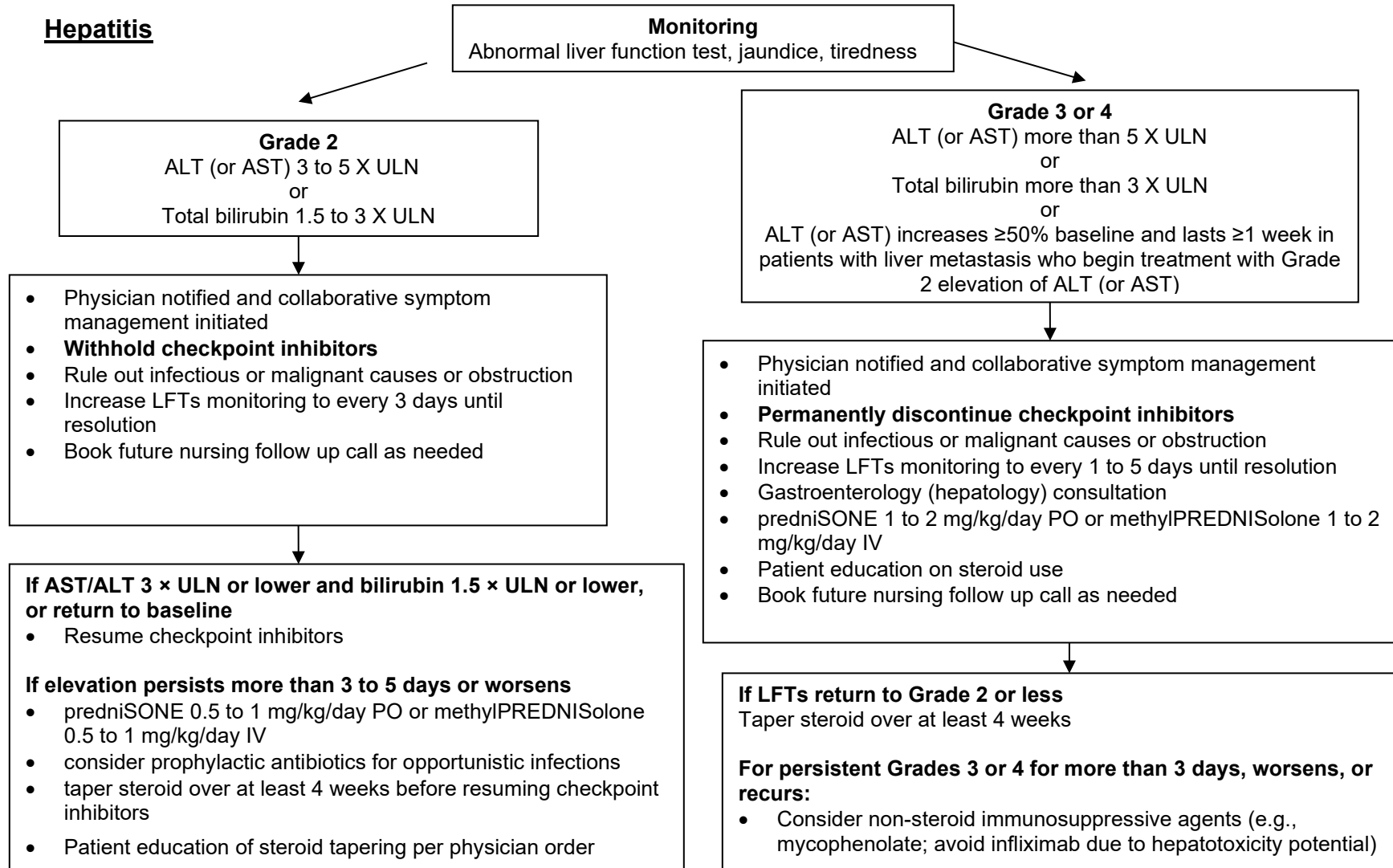
## **Pneumonitis**



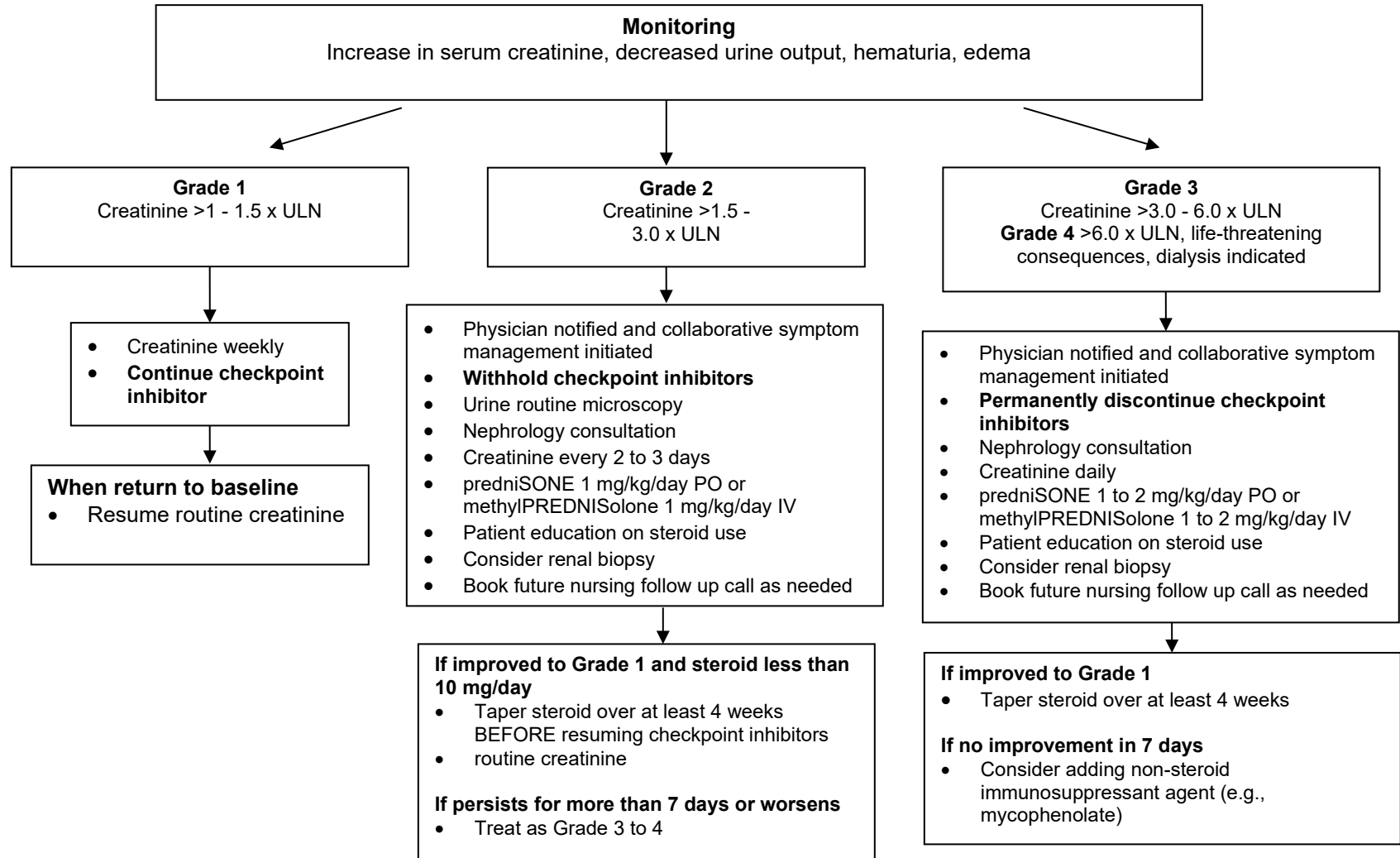
## Enterocolitis



## Hepatitis



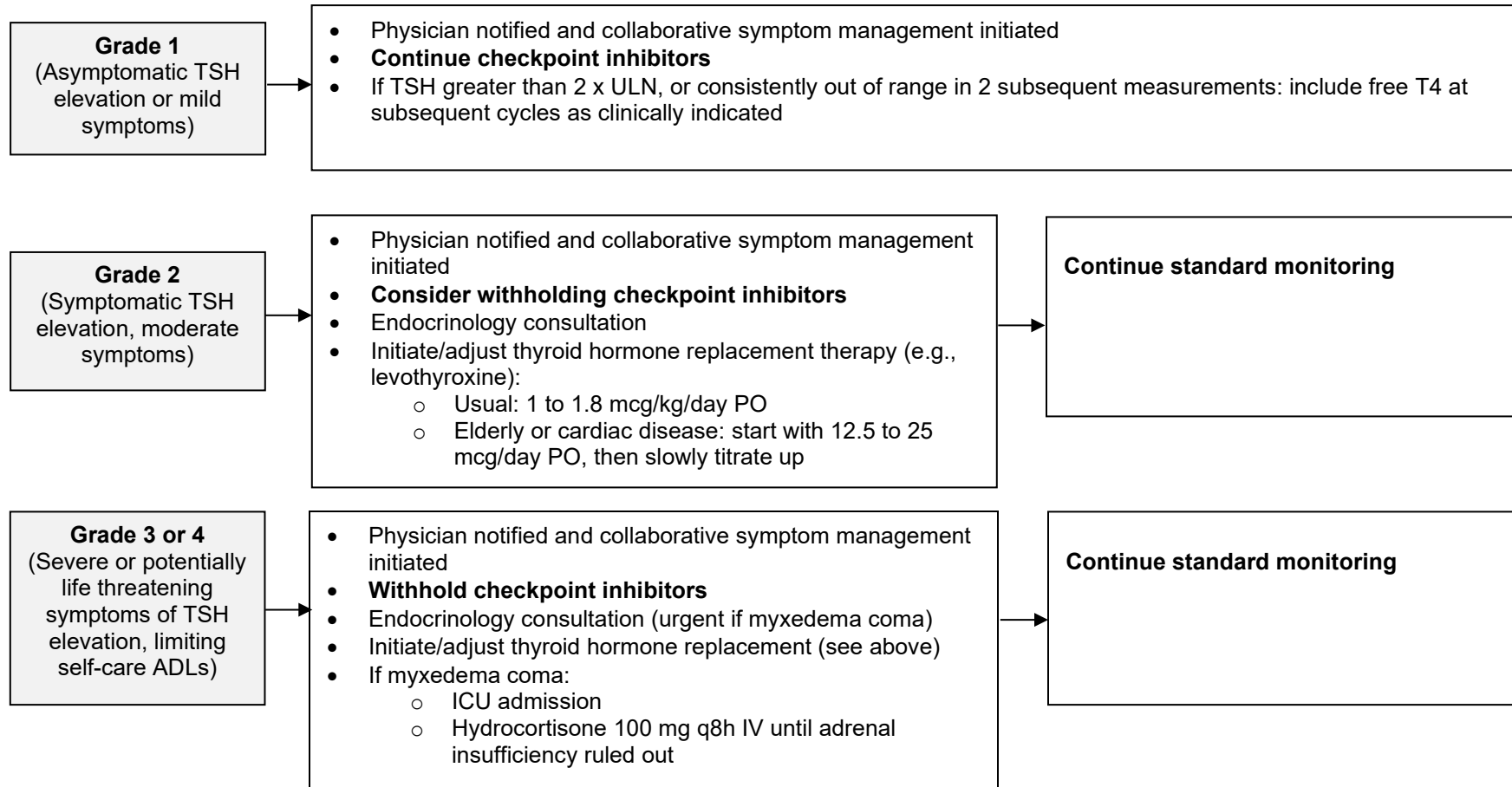
## Nephritis



## **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

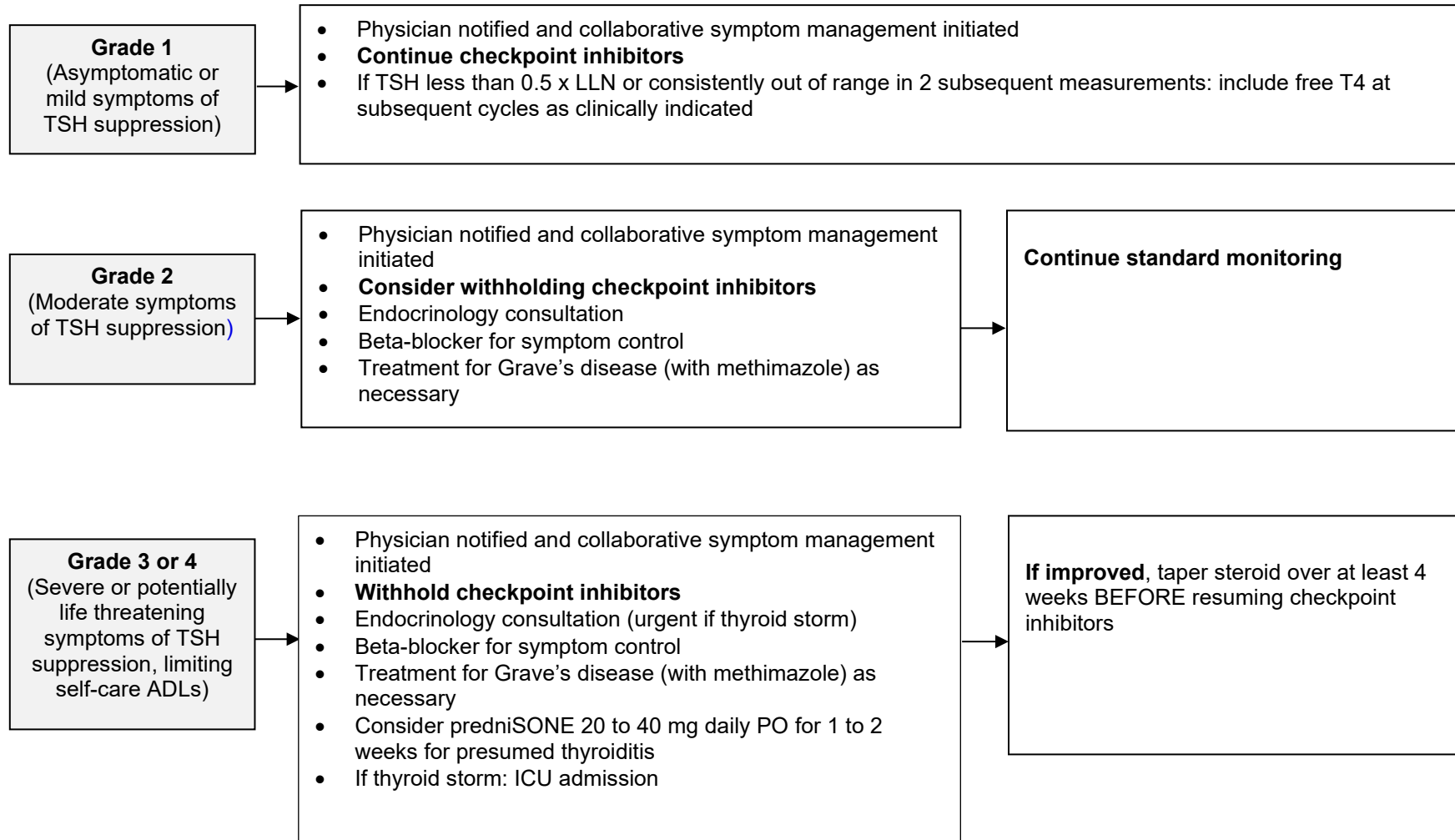




## Endocrine: Hyperthyroidism

### Monitoring

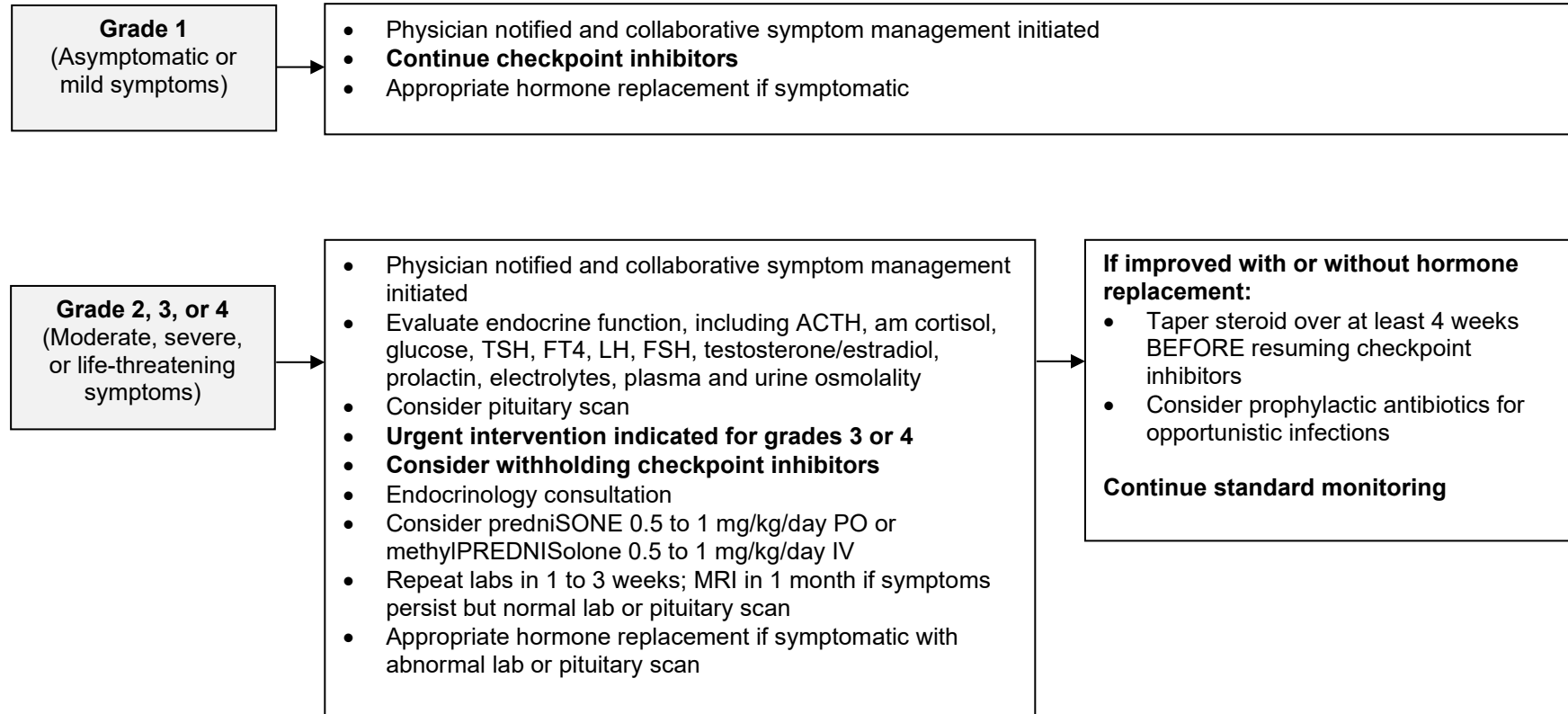
Weight loss, increased frequency of bowel movements, heat intolerance, sweating, tremor, palpitations, anxiety, fatigue, goiter



## **Endocrine: Hypophysitis**

### **Monitoring**

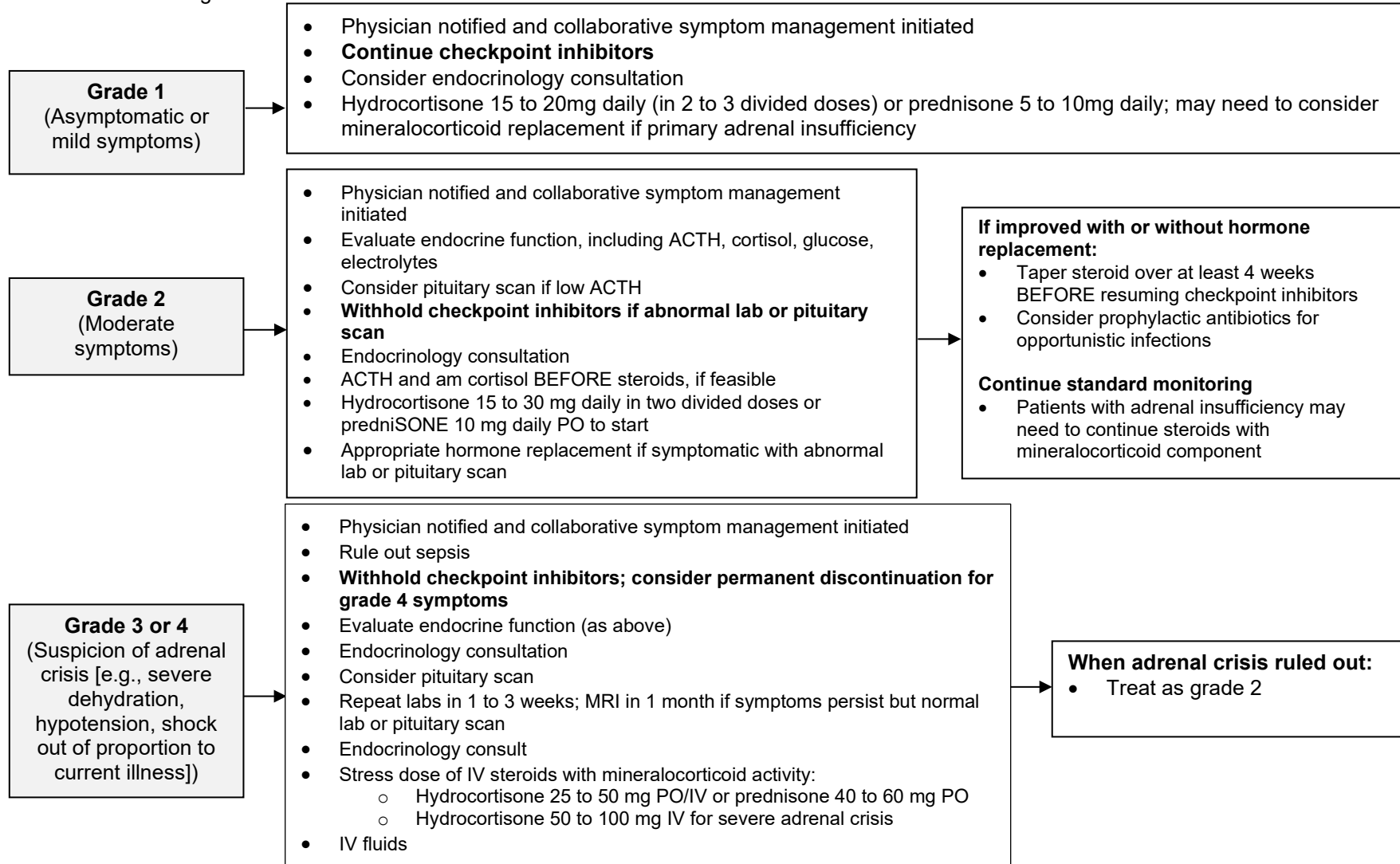
Persistent or unusual headaches, vision changes, extreme tiredness, weight gain or loss, mood or behaviour changes (e.g., decreased libido, confusion, forgetfulness), dizziness or fainting, hair loss, feeling cold, constipation, hoarseness



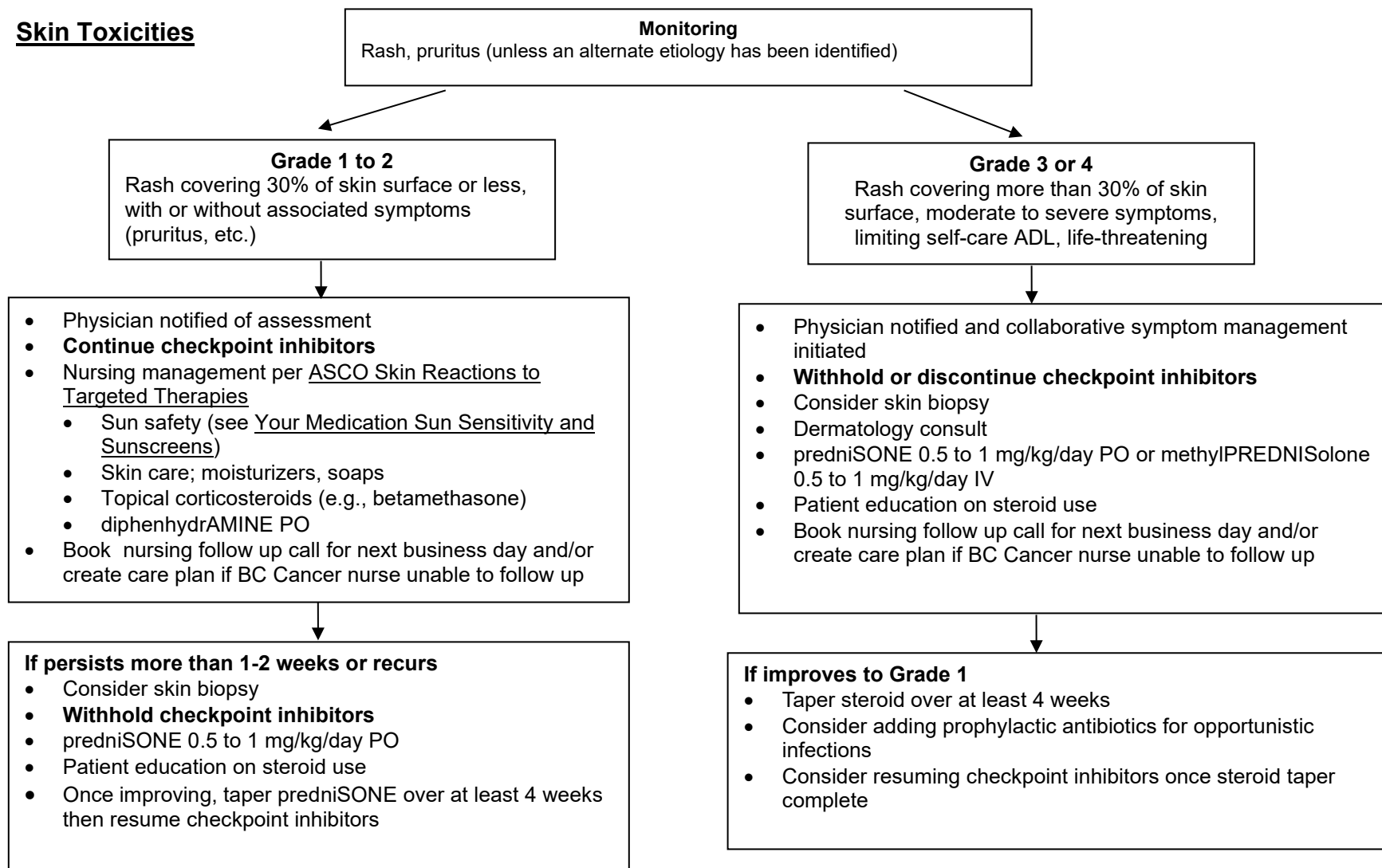
## Endocrine: Adrenal Insufficiency

### Monitoring

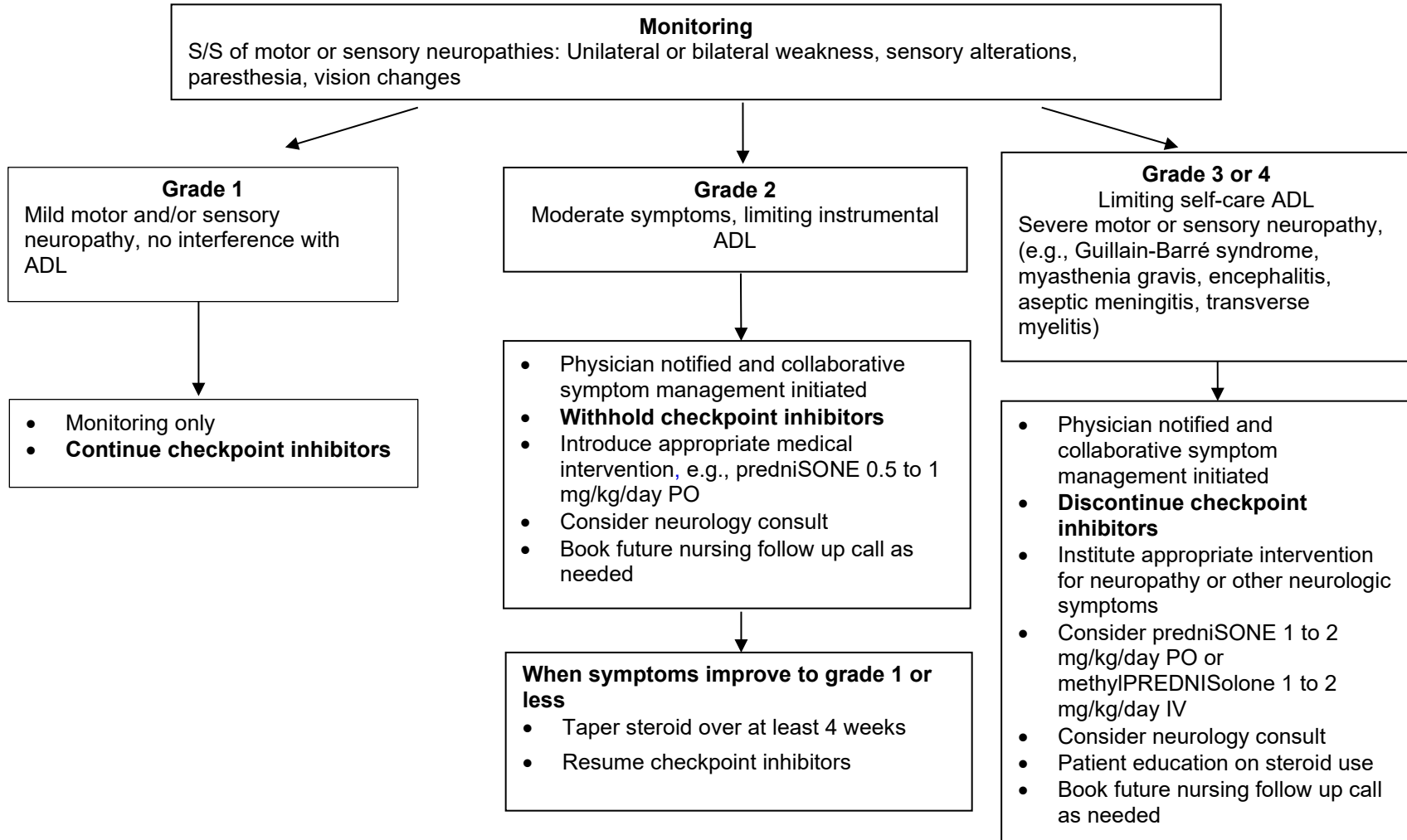
Persistent or unusual headaches, extreme tiredness, weakness, dehydration, mood or behaviour changes (e.g., confusion, forgetfulness), dizziness or fainting



## **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
<b>Pneumonitis</b>	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
<b>Enterocolitis</b>	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
<b>Hepatitis</b>		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 $\geq 50\%$ baseline and lasts $\geq 1$ week in patients with liver metastasis who begin treatment with Grade 2 elevation of ALT (or AST)
<b>Nephritis</b>	Creatinine $>1 - 1.5 \times$ ULN	Creatinine $>1.5 - 3.0 \times$ ULN	Creatinine $>3.0 - 6.0 \times$ ULN	Creatinine $>6.0 \times$ ULN, life-threatening consequences, dialysis indicated
<b>Hypothyroidism</b>	Asymptomatic TSH elevation or mild symptoms	Symptomatic TSH elevation, moderate symptoms	Severe symptoms of TSH elevation	Potentially life threatening symptoms of TSH elevation
<b>Hyperthyroidism</b>	Asymptomatic or mild symptoms of TSH suppression	Moderate symptoms of TSH suppression	Severe symptoms of TSH suppression	Potentially life threatening symptoms of TSH suppression
<b>Hypophysitis</b>	Asymptomatic or mild symptoms	Moderate symptoms	Severe symptoms	Life-threatening symptoms
<b>Adrenal Insufficiency</b>	Asymptomatic or mild symptoms	Moderate symptoms	Suspicion of adrenal crisis (e.g., severe dehydration, hypotension, shock out of proportion to current illness)	

<b>Immune-Related Adverse Events</b>	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
<b>Skin Toxicities</b>	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	
<b>Neurologic Toxicities</b>	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)	