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ALGORITHM FOR SUSPECTED IMMUNE-RELATED ADVERSE EVENTS

General recommendations for management of suspected immune related adverse events

Caution: With the appearance of any generalized rash, discontinue and avoid any concomitant medications (eg, antibiotics, anticonvulsants, or proton pump inhibitors) that may be associated with severe skin reactions.

Suspicion of an immune related adverse event (irAE)+

Rule-out non-immune related causes

If symptoms have a GI, Liver, or Endocrine etiology, then refer to "Diarrhea," "Hepatotoxicity," or "Endocrinopathy" Management Algorithm for more specific guidance

What is the severity of the adverse event? (NCI CTCAE grading)

Low grade (Grade 1 or 2)

- Increase monitoring
- Symptomatic treatment
- Consider skipping next dose until event resolves
- Consider oral steroid therapy** for persistent or recurring Grade 2 irAEs
- If symptoms worsen or do not improve with treatment after 1-2 weeks then consider managing as a high grade event

High grade (Grade 3 or 4)

- Increase monitoring
- Strongly consider high-dose steroid therapy**
- Hold further dosing until adverse event resolves
- Consider specialist consult
- If steroid therapy is initiated and symptoms improve, then consider a gradual steroid taper over 4 weeks
- If symptoms do not respond within 5-7 days of intervention, then consider alternative immunosuppression therapy (eg, mycophenolate mofetil, tacrolimus, infliximab)

+ **Definition: irAEs are associated with ipilimumab exposure and are consistent with immune phenomenon**

Examples of possible irAEs *(common and rare)*: rash, pruritus, diarrhea/colitis, hepatitis/elevated liver function tests, hypopituitarism, hypo/hyperthyroidism, uveitis, pneumonitis, nephritis, pancreatitis, aseptic meningitis, toxic epidermal necrolysis, myopathy/myositis or neuromuscular disorder (eg, myasthenia gravis, Guillain-Barré syndrome)*

***A complete list of irAEs can be found in Section 5.6 of the Investigator Brochure**

****Based on clinical experience to date, systemic steroids for treatment of irAEs do not appear to impact the development or maintenance of ipilimumab clinical activity in advanced melanoma**

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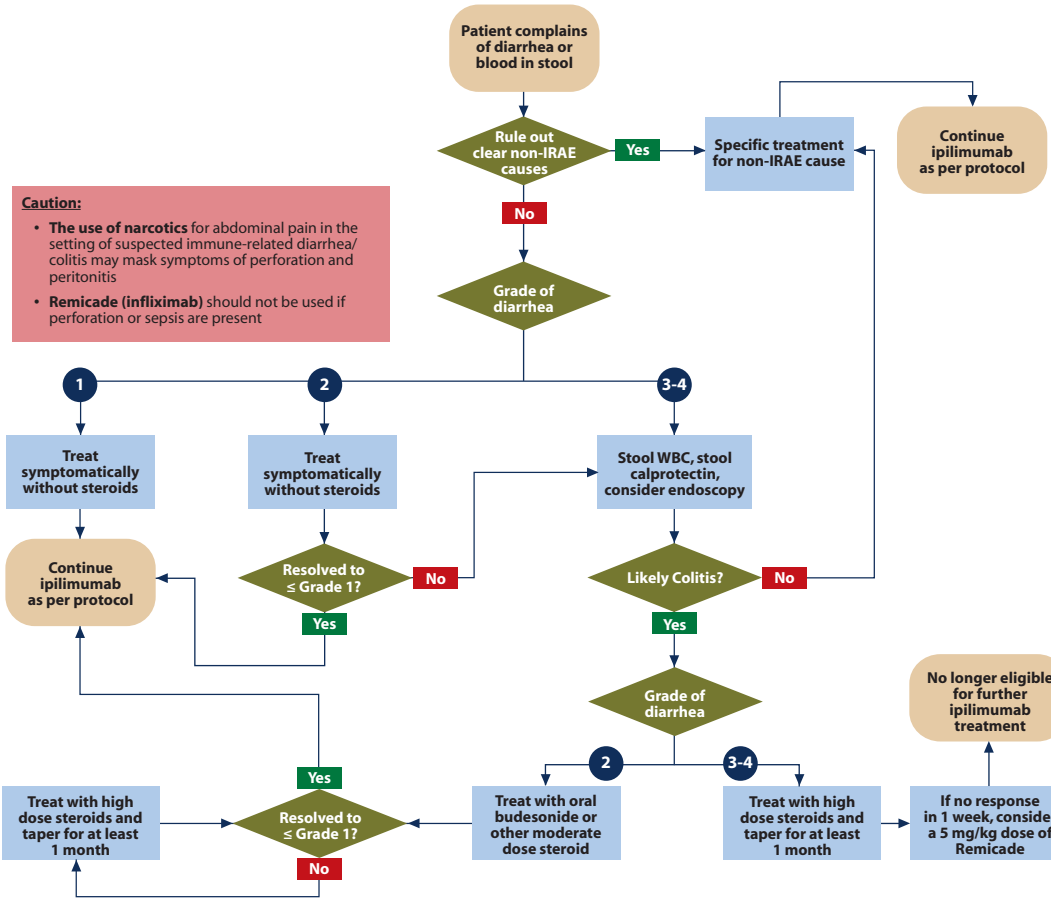
DIARRHEA MANAGEMENT ALGORITHM



	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared with baseline	Increase of 4-6 stools per day over baseline; IV fluids indicated <24 hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL	Life-threatening consequences (eg, hemodynamic collapse)	Death

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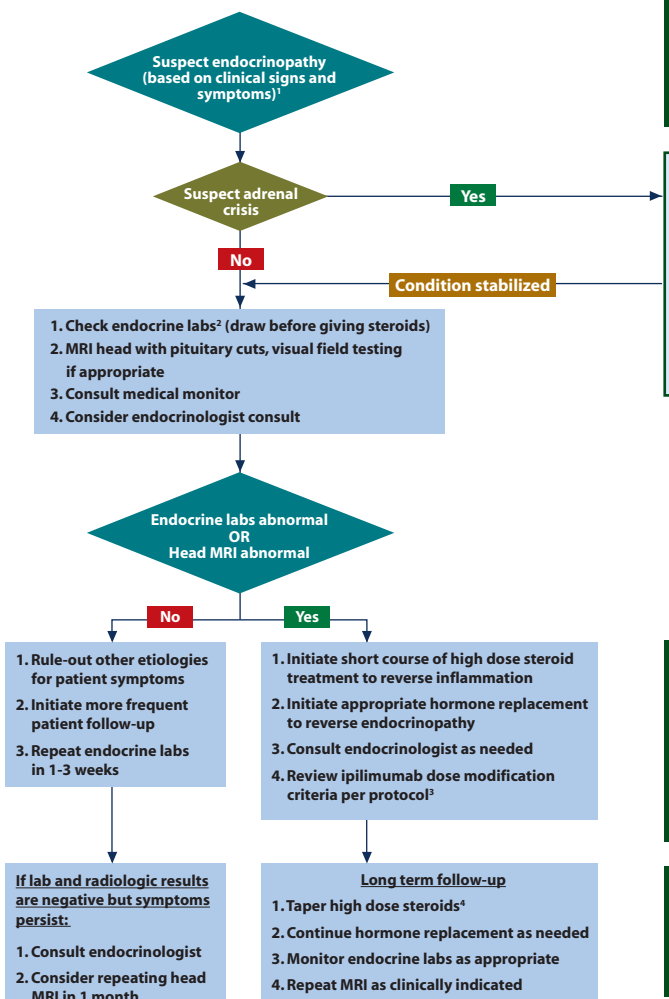
ENDOCRINOPATHY MANAGEMENT ALGORITHM



[1]Clinical signs and symptoms that may be indicative of underlying endocrinopathy:

Headache, visual field defects, fatigue, weakness, asthenia, failure to thrive, anorexia, nausea and vomiting, lethargy, impotence, amenorrhea, fever, coma, new onset atrial fibrillation, hypotension, hypoglycemia, hyponatremia, eosinophilia

Suspect Adrenal Crisis

1. Rule out sepsis
2. If strong suspicion of adrenal crisis (eg, exhibits signs of severe dehydration, hypotension, or shock out of proportion to severity of current illness) then start stress dose IV steroids (with mineralocorticoid activity), fluids, consult endocrinologist
3. If symptoms suggestive of endocrinopathy but patient is not in crisis then it may be appropriate to wait for lab results before starting steroid therapy

[2]Suggested endocrine lab work:

1. TSH, free T4, T3
2. ACTH, AM serum cortisol → if abnormal, co-syntropin stimulation test
3. LH, FSH, testosterone, prolactin

[3]Ipilimumab dosing:

a) Upon resolution or adequate treatment of endocrinopathy, patients may continue ipilimumab dosing with appropriate hormone replacement unless limited by the protocol

b) The risk of having a recurrence of endocrinopathy with subsequent ipilimumab dosing after experiencing initial IRAE is currently unknown

[4]Prolonged replacement steroid therapy:

a) Patients may require chronic hydrocortisone replacement to maintain homeostatic levels

b) Beware of complete discontinuation of steroids due to prolonged adrenal suppression

For numbered footnotes ([1,2,3,4]), please refer to further explanation and text found in the corresponding green to the right of the algorithm.

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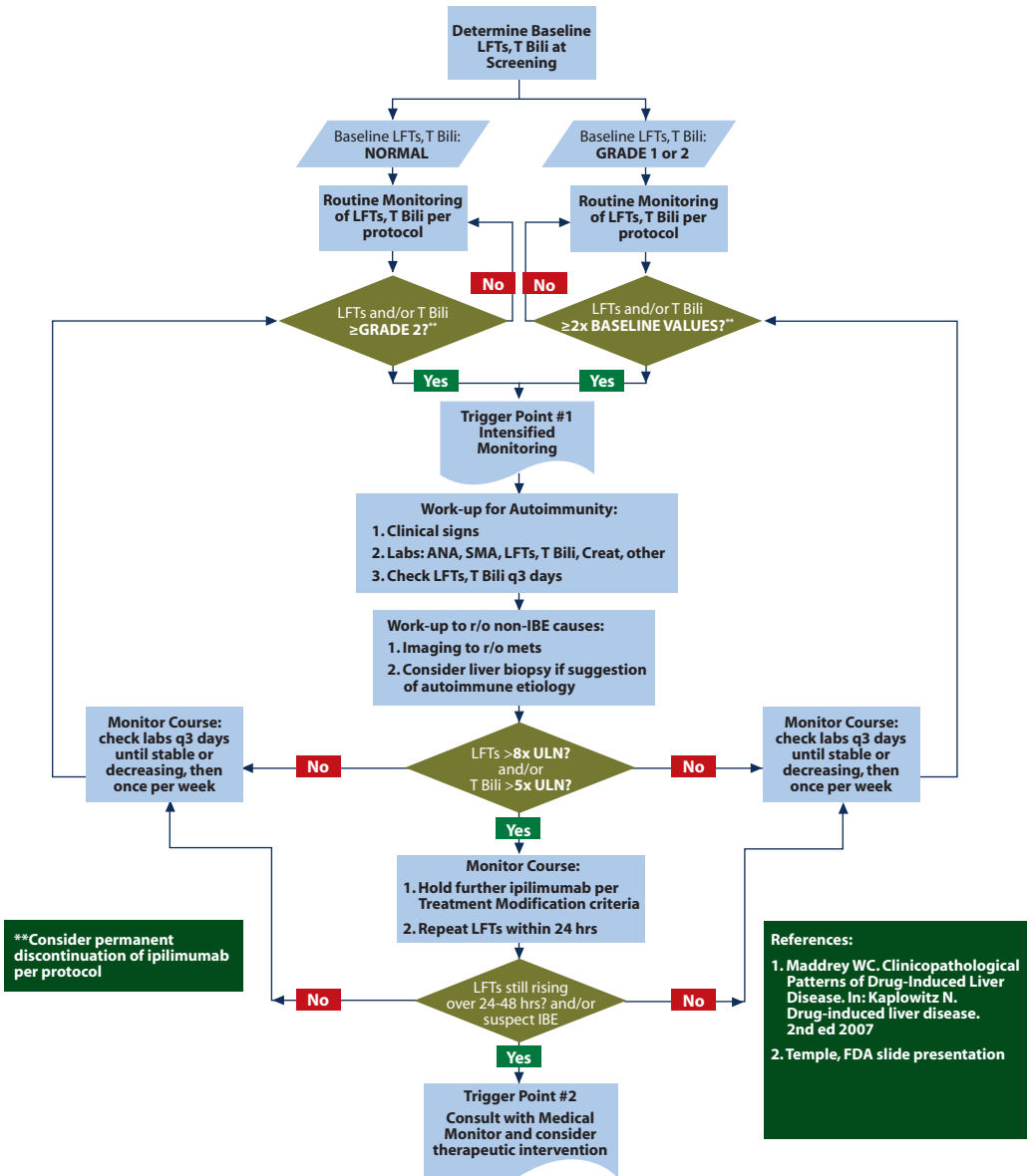
HEPATOTOXICITY MANAGEMENT ALGORITHM



**Consider permanent discontinuation of ipilimumab per protocol

References:

1. Maddrey WC. Clinicopathological Patterns of Drug-Induced Liver Disease. In: Kaplowitz N. Drug-induced liver disease. 2nd ed 2007
2. Temple, FDA slide presentation

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HEPATOTOXICITY THERAPEUTIC INTERVENTION ALGORITHM

The most current experience with immune-related hepatitis has allowed further development of this management algorithm to include recommendations for treatment.

Situation: rising liver function tests (LFTs) >8x ULN or suspected immune-mediated hepatitis

1) Admit subject to hospital for evaluation and close monitoring
2) Stop further ipilimumab dosing until hepatotoxicity is resolved. Consider permanent discontinuation of ipilimumab per protocol
3) Start at least 120 mg methylprednisolone sodium succinate per day, given IV as a single or divided dose
4) Check liver laboratory test values (LFTs, T-bilirubin) daily until stable or showing signs of improvement for at least 3 consecutive days
5) If no decrease in LFTs after 3 days or rebound hepatitis occurs despite treatment with corticosteroids, then add mycophenolate mofetil 1 g BID per institutional guidelines for immunosuppression of liver transplants (supportive treatment as required, including prophylaxis for opportunistic infections per institutional guidelines)
6) If no improvement after 5 to 7 days, consider adding 0.10 to 0.15 mg/kg/day of tacrolimus (trough level 5-20 ng/mL)
7) If target trough level is achieved with tacrolimus but no improvement is observed after 5 to 7 days, consider infliximab, 5 mg/kg, once
8) Continue to check LFTs daily for at least 2 weeks to monitor sustained response to treatment

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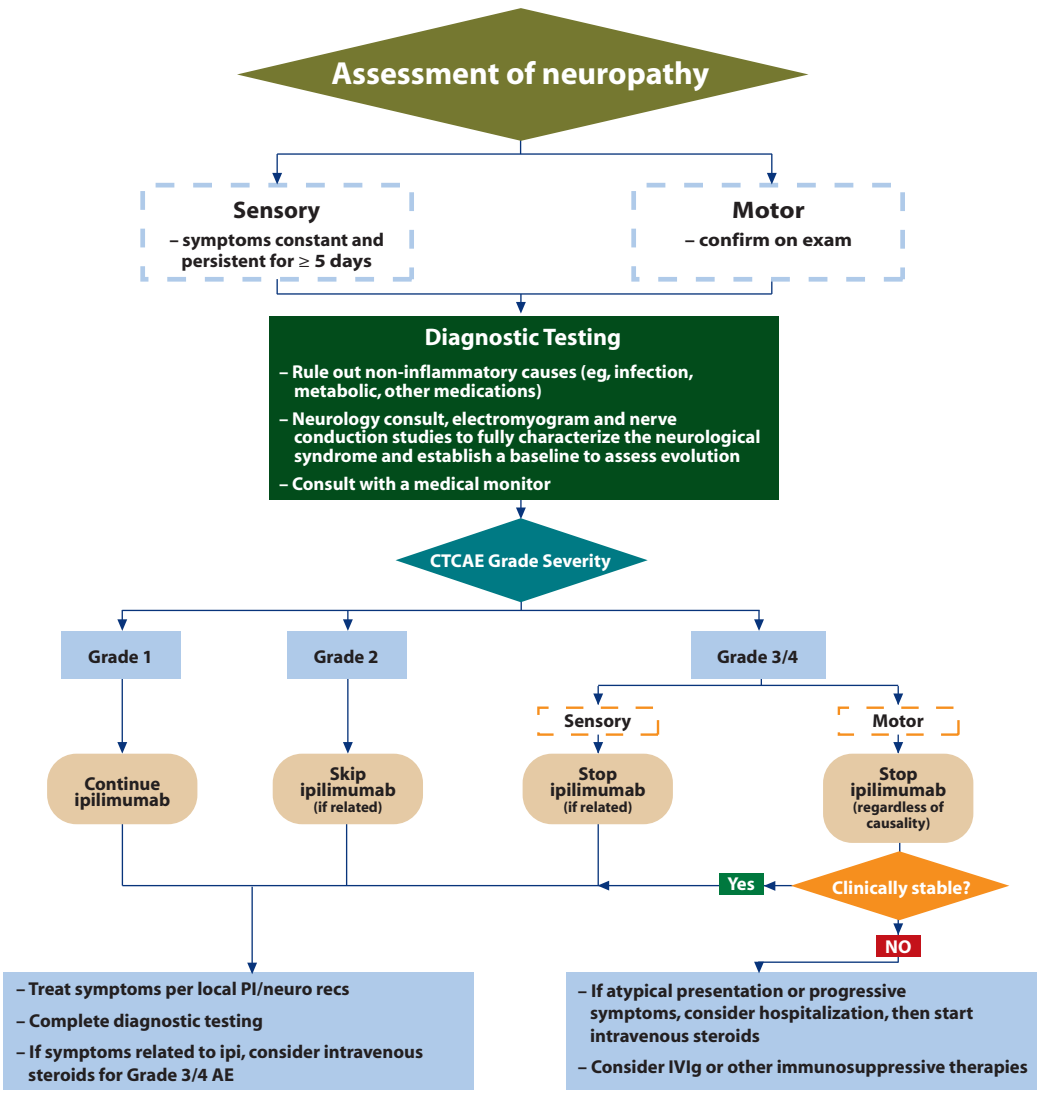
NEUROPATHY MANAGEMENT ALGORITHM



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