**Algorithm for Suspected Immune-Related Adverse Events**

**General recommendations for management of suspected immune related adverse events**

- 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

**Suspicion of an immune related adverse event (irAE)**

- Rule out non-immune related causes

**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

**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 (e.g., mycophenolate mofetil, tacrolimus, infliximab)

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

Examples of possible irAEs: rash, pruritus, diarrhea/colitis, hepatitis, endocrinopathy, pneumonitis, nephritis, pancreatitis, myopathy/myositis, aseptic meningitis, Guillain-Barré syndrome, or Guillain-Barré syndrome-like syndrome.

**Suspicious signs that may be associated with immune related reactions**

- General symptoms: constitutional (fever, chills, fatigue, malaise), dermatologic (rash, pruritus), pulmonary (dyspnea, cough), hepatic (elevation of liver function tests), endocrinologic (hypothyroidism, hyponatremia, hypertension), gastrointestinal (diarrhea, stomatitis), neurologic (myasthenia gravis, cramps, weakness, tremors, altered mental status), ocular (uveitis, orbital pseudotumor, episcleritis, keratitis, conjunctivitis, retinal vein occlusion), musculoskeletal (myopathy, myositis, myalgia, arthritis), cardiac (pericarditis, myocarditis), hematologic (anemia, neutropenia, thrombocytopenia), gastrointestinal (ulcerative proctitis, colitis, cramping, diarrhea, nausea, vomiting), nephrologic (proteinuria, hematuria, urinary tract infection), neurologic (seizures, psychosis, delirium), endocrine (hyper/hypothyroidism, gonadal failure), cutaneous (lichen planus, vasculitis, bullae, purpura, erythema nodosum), pulmonary (pneumonitis, pleural effusion, pneumothorax), gastrointestinal (diarrhea, vomiting, ileus), cardiac (cardiomyopathy, pericarditis), hematologic (pallor, bruising, pale skin, petechiae), skin (alopecia, rash, pruritus, desquamation), neurologic (ataxia, tremor, myopathy, neuropathy, peripheral neuropathy).

**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

**Notes**

- A complete list of irAEs can be found in Section 5.6 of the Investigator Brochure
- Caution: With the appearance of any generalized rash, discontinue and avoid any concomitant medications that may be associated with severe skin reactions.
- Please refer to the most recent version of the Investigator Brochure for additional information.

**Version Date:** 04/10
Diarrhea Management Algorithm

### Diarrhea Grades

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Increase of &lt;4 stools per day over baseline; mild increase in ostomy output compared to baseline</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Increase of 4-6 stools per day over baseline; IV fluids indicated; &lt;24 hr moderate increase in ostomy output compared to baseline; not interfering with ADL</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Increase of ≥7 stools per day over baseline; hospitalization; ≥24 hr severe increase in ostomy output compared to baseline; interfering with ADL</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Life-threatening consequences (e.g., hemodynamic collapse)</td>
</tr>
<tr>
<td>Grade 5</td>
<td>Death</td>
</tr>
</tbody>
</table>

### Specific Treatments

- **Grade 1**: Continue ipilimumab as per protocol
- **Grade 2**: Continue ipilimumab as per protocol
- **Grade 3**: No longer eligible for further ipilimumab treatment
- **Grade 4**: No longer eligible for further ipilimumab treatment

### Additional Notes

- **Special Notes**: Diarrhea management algorithm for ipilimumab treatment.
- **Reminders**: The use of narcotics for abdominal pain in the setting of suspected immune-related diarrhea/colitis may mask symptoms of perforation and peritonitis. Remicade (infliximab) should not be used if perforation or sepsis are present.

### Version Date

- Version Date: 04/10

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**Disclaimer:**

Please refer to the most recent version of the Investigator brochure for additional information.
Suspect adrenal crisis
1. Rule out other etiologies for patient symptoms
2. Initiate more frequent patient follow-up
3. Repeat endocrine labs in 1-3 weeks
4. If lab and imaging results for patient symptoms are negative:
   1. Check endocrine labs (draw before giving steroids)
   2. MRI head with pituitary cuts, visual field testing if appropriate
   3. Consult neuro-ophthalmologist
   4. Consider endocrinologist consult

Suspect endocrinopathy
1. Rule out adrenal crisis
2. If strong suspicion of adrenal crisis (eg, exhibits signs of severe dehydration, hypotension, or shock, not all 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

Endocrine labs abnormal OR Head MRI abnormal
1. Initiate short course of high dose steroid treatment to reverse inflammation
2. Initiate appropriate hormone replacement to reverse endocrinopathy
3. Consult endocrinologist as needed
4. Review ipilimumab dose modification criteria per protocol

Condition stabilized
1. Check endocrine labs (draw before giving steroids)
2. MRI head with pituitary cuts, visual field testing if appropriate
3. Consult medical monitor
4. Consider endocrinologist consult
5. Repeat MRI as clinically indicated

If lab and radiologic results are negative but symptoms persist:
1. Consult endocrinologist
2. Consider repeating head MRI in 1 month

Suggested endocrine lab work:
1. TSH, free T4, T3
2. ACTH, AM serum cortisol
3. LH, FSH, testosterone, prolactin

Long term follow-up
1. Taper high dose steroids
2. Continue hormone replacement as needed
3. Monitor endocrine labs as appropriate
4. Repeat MRI as clinically indicated

Additional comments:
- If adrenal crisis is ruled out, consider alternative diagnoses and appropriate workup.
- Consider endocrinologic consultation for persisting endocrinopathy.
- Monitor for recurrence of endocrinopathy.

Prolonged replacement steroid therapy:
- Patients may require chronic hydrocortisone replacement to maintain homeostatic levels.
- Beware of complete discontinuation of steroids due to prolonged adrenal suppression.

Ipilimumab dosing:
- Upon resolution or adequate treatment of endocrinopathy, patients may continue ipilimumab dosing with appropriate hormone replacement unless limited by the protocol.
- The risk of having a recurrence of endocrinopathy with subsequent ipilimumab dosing after experiencing initial IRAE is currently unknown.

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Please refer to the most recent version of the Investigator brochure for additional information.
HEPATOTOXICITY MANAGEMENT ALGORITHM

**Consider permanent discontinuation of ipilimumab per protocol**

**LFTs and/or T Bili ≥ GRADE 2?**

- **No**
  - Baseline LFTs, T Bili: NORMAL
  - Baseline LFTs, T Bili: GRADE 1 or 2
  - Routine Monitoring of LFTs, T Bili per protocol

- **Yes**
  - Trigger Point #1: Intensified Monitoring
    - Work-up for Autoimmunity:
      1. Clinical signs
      2. Labs: ANA, SMA, LFTs, T Bili, Creat, other
      3. Check LFTs, T Bili at Days
    - Work-up to rule out non-IBE causes:
      1. Imaging to rule out causes
      2. Consider bone biopsy if suggestion of autoimmunity unlikely
    - Monitor Course:
      1. Hold further ipilimumab per Treatment Modification criteria
      2. Repeat LFTs within 24 hrs
      3. Monitor LFTs, T Bili q3 days until stable or decreasing, then once per week
      4. Repeat if necessary

**LFTs and/or T Bili ≥ 2x BASELINE VALUES?**

- **No**
  - Yes

- **Yes**
  - LFTs > 8x ULN and/or T Bili > 5x ULN
  - Monitor Course:
    1. Repeat LFTs, T Bili q3 days until stable or decreasing, then once per week
    2. Consider permanent discontinuation of ipilimumab per protocol
    3. Trigger Point #2: Consult with Medical Monitor and consider immunosuppressive intervention

References:
2. Temple, FDA slide presentation

**Consider permanent discontinuation of ipilimumab per protocol**

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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
NEUROPATHY MANAGEMENT ALGORITHM

Assessment of neuropathy

Sensory
- symptoms constant and persistent for > 5 days

Motor
- confirm on exam

Diagnostic Testing
- Rule out non-inflammatory causes (e.g., infection, metabolic, other medication)
- Neurology consult, electromyogram and nerve conduction studies to fully characterize the neurological syndrome and establish a baseline to assess evolution
- Consult with a medical monitor

CTCAE Grade Severity

Grade 1
- Treat symptoms per local PI/neuro recs
- Complete diagnostic testing
- If symptoms related to ipi, consider intravenous steroids for Grade 3/4 AE

Grade 2
- If atypical presentation or progressive symptoms, consider hospitalization, then start intravenous steroids
- Consider IVlg or other immunosuppressive therapies

Grade 3/4
- Stop ipilimumab (regardless of causality)

Clinically stable?

Yes

No

Motility
- confirm on exam

Sensory
- symptoms constant and persistent for > 5 days

Continue ipilimumab

Skip ipilimumab (5 months)

Stop ipilimumab (5 months)

Stop ipilimumab (regardless of causality)

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Please refer to the most recent version of the Investigator brochure for additional information.