**Evaluation and Management of Suspected Immune-Mediated Colitis/Diarrhea**

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**GENERAL EVALUATION**

**PRESENTATION**

- Patient presents with new onset of diarrhea 1 week after immunotherapy initiation and up to 6 months after last dose of immunotherapy.

**ASSESSMENT**

- Hold immunotherapy and order the following:
  - GI consult
  - GI Multiplex PCR panel and fecal CMV PCR
  - Consider infectious workup for non-GI organs if there is fever or symptoms suggesting individual organ involvement
  - CT abdomen/pelvis with oral and IV contrast
  - Laboratory evaluation: CBC, complete metabolic panel (CMP), amylase, lipase, and ANA
  - Inflammatory blood markers: ESR and CRP
  - Inflammatory stool markers: lactoferrin and calprotectin
  - Fecal pancreatic elastase to rule out exocrine pancreatic insufficiency
  - Total IgA and tissue transglutaminase (tTG) IgA to rule out celiac disease
  - Screening tests, if not drawn within the past 6-12 months

**TREATMENT**

- For recurrent colitis/diarrhea assessment and treatment, see Page 5

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1. Diarrhea is defined as the presence of 3 or more unformed stools a day.
2. On rare occasions, GI toxicities may develop beyond the typical 6 month window.
3. PD-1 inhibitors (pembrolizumab, nivolumab), PD-L1 inhibitors (atezolizumab, avelumab, durvalumab), CTLA-4 inhibitor (ipilimumab).
4. Colitis symptoms include abdominal pain, rectal bleeding, and blood or mucus in stools.
5. Refer to Appendix A for Modified Common Terminology Criteria for Adverse Events (CTCAE).
6. Fecal CMV PCR has low sensitivity and poor negative predictive value for the diagnosis of CMV colitis. Consider early colonoscopy in immunosuppressed patients to exclude CMV colitis and perform colonoscopy in patient with positive fecal CMV by PCR.
7. Screening tests include HIV antibody; T-spot tuberculosis; hepatitis A, B and C panel; and urine Histoplasma antigen.

CMV = cytomegalovirus
ANA = antinuclear antibodies

For further assessment/management, see Page 2

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### GENERAL EVALUATION - continued

#### PRESENTATION

Other causes(s) for colitis excluded

#### ASSESSMENT

Is the CT abdomen positive for colitis/enteritis or are there positive inflammatory markers?  

- Yes
- No

#### ENDOSCOPY FINDINGS

**Low-risk features:**
- Normal colon appearance and normal histology

**Moderate-risk features:**
- Normal colon appearance with pathology showing inflammation
- Focal erythema, friability, or loss of vascularity
- No ulcerations
- No infection identified on biopsy

**High-risk features:**
- Presence of ulcerations
- Diffuse inflammation along entire colon
- No infection identified on biopsy

EGD results with confirmed inflammation to stomach and duodenum

Refer to assessment and treatment of diarrhea on Page 4

For management of lower GI toxicity/colitis, see Page 3

For upper GI management, see Page 6

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**EGD** = esophagogastroduodenoscopy

1. Stool: lactoferrin and calprotectin; blood: ESR and CRP
2. Perform colonoscopy and EGD only if ANC greater than 0.5 K/microliter
3. Examine biopsies for the presence of CMV and other opportunistic infections in immunosuppressed patients
4. Order EGD if there are signs and symptoms of concurrent nausea/vomiting and/or epigastric pain

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Resume immunotherapy (PD-1 or PD-L1) after completion of corticosteroids

- Consider longer duration of infliximab or vedolizumab
- Consider fecal microbiota transplant (FMT)
- Consider repeat colonoscopy if colitis symptoms develop
  (For endoscopy findings and subsequent management, see Page 2)

ENDOSCOPY FINDINGS

Low-risk features

- Corticosteroid\(^1\) with taper for total treatment duration less than 30 days
- If refractory to corticosteroids after 3 days, consider one dose of infliximab or vedolizumab

Clinical follow-up for recurrent clinical symptoms

- Clinical remission achieved?
  - Yes
    - Resume immunotherapy (PD-1 or PD-L1) after completion of corticosteroids
  - No
    - Consider longer duration of infliximab or vedolizumab
    - Consider fecal microbiota transplant (FMT)
    - Consider repeat colonoscopy if colitis symptoms develop

Corticosteroids\(^2\) and start infliximab or vedolizumab within one week of corticosteroid initiation

Repeat colonoscopy\(^3\) after 3 doses of infliximab or vedolizumab (8-10 weeks after initiation)

Response seen on colonoscopy?

- Yes
  - Continue infliximab or vedolizumab until resolution of inflammation on repeat endoscopy
  - Resume immunotherapy\(^4\) (PD-1 or PD-L1) after improvement of mucosal inflammation confirmed by repeat endoscopy
- No
  - Consider early repeat colonoscopy after 2 doses of infliximab or vedolizumab if symptoms persist

Symptom improvement?\(^5\)

- Yes
  - Discontinue infliximab or vedolizumab if immunotherapy is not resumed\(^4\)
  - Consider repeat GI Multiplex PCR panel if more than 1 week after first test
- No
  - Consider FMT or Consult surgery

\(^1\) May consider budesonide as an additional option
\(^2\) Start steroid taper over 2 weeks after starting infliximab or vedolizumab (total corticosteroid treatment duration should be less than 30 days)
\(^3\) Consider early repeat colonoscopy after 2 doses of infliximab or vedolizumab if symptoms persist
\(^4\) If resuming immunotherapy, continue long-term vedolizumab concurrently

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\(\text{Page 3 of 9}\)
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DIARRHEA MANAGEMENT

PRESENTATION

Diarrhea without signs or symptoms of colitis

Mild diarrhea (Grade 1)

Moderate and severe diarrhea (Grade 2 and above)

ASSESSMENT/TREATMENT

Hold immunotherapy and order the following:
- GI Multiplex PCR panel and fecal CMV PCR
- Laboratory evaluation: CBC, CMP, and ANA
- Inflammatory blood markers: ESR and CRP
- Inflammatory stool markers: lactoferrin and calprotectin
- Fecal pancreatic elastase to rule out exocrine pancreatic insufficiency
- Total IgA and tissue transglutaminase (tTG) IgA to rule out celiac disease
- Screening tests, if not drawn within the past 6-12 months

While test results are pending:
- Encourage hydration (2-3 liters per day)
- Initiate bland diet
- Consider mesalamine 2.4-4.8 grams/day until culture results return
- Consider hospitalization if inadequate hydration orally

 Improvement seen within one week?

Yes

Resume previous immunotherapy, if held

No

Hold immunotherapy (if not already held) if severity progresses to Grade 2 diarrhea (see moderate diarrhea management below)

Alternate causes(s) of diarrhea found?

Yes

- Initiate appropriate therapy
- Consider Infectious Diseases and/or GI consult as appropriate

No

Treat as non-infectious colitis (see Box A on Page 2)

1 Colitis symptoms include abdominal pain, rectal bleeding, and blood or mucus in stools
2 Refer to Appendix A for Modified Common Terminology Criteria for Adverse Events (CTCAE)
3 Fecal CMV PCR has low sensitivity and poor negative predictive value for the diagnosis of CMV colitis. Consider early colonoscopy in immunosuppressed patients to exclude CMV colitis and perform colonoscopy in patients with positive fecal CMV by PCR.
4 Consider anti-motility agents only if non-invasive pathogens have been excluded
5 Screening tests include HIV antibody; T-spot tuberculosis; hepatitis A, B and C panel; and urine Histoplasma antigen
6 If cultures return negative and/or no improvement is seen after 2 days of treatment, discontinue mesalamine and consider starting corticosteroids. If patient has symptom improvement with mesalamine, continue treatment regardless of culture results.

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RECURRENT MANAGEMENT

ASSESSMENT

Hold immunotherapy and order the following:
- GI Multiplex PCR panel and fecal CMV PCR
- Laboratory evaluation: CBC, CMP, amylase, and lipase
- Inflammatory blood markers: ESR and CRP
- Inflammatory stool markers: lactoferrin and calprotectin
- Fecal pancreatic elastase to rule out exocrine pancreatic insufficiency

Optional workup:
- Consider infectious workup for non-GI organs if there is fever or symptoms suggesting individual organ involvement
- Screening tests, if not drawn within the past 6-12 months
- CT abdomen with oral and IV contrast

TREATMENT

Alternate cause(s) of colitis/diarrhea found?

Yes

- Initiate appropriate therapy
- Consider Infectious Diseases and/or GI consult as appropriate

No

Colonoscopy or flex sigmoidoscopy with biopsy

For endoscopy findings and subsequent management, see Page 2

1 Refer to Appendix A for Modified Common Terminology Criteria for Adverse Events (CTCAE)

2 Fecal CMV PCR has low sensitivity and poor negative predictive value for the diagnosis of CMV colitis. Consider early Colonoscopy in immunosuppressed patients to exclude CMV colitis and perform colonoscopy in patients with positive fecal CMV by PCR.

3 Screening tests include HIV antibody; T-spot tuberculosi; hepatitis A, B and C panel; and urine Histoplasma antigen

4 If initial colonoscopy confirmed left colon involvement, then consider flex sigmoidoscopy on follow-up
UPPER GI MANAGEMENT

ASSESSMENT/TREATMENT

- Proton pump inhibitor (PPI) for 2 weeks trial and
- Rule out other factors for inflammation (i.e., infection, recent NSAID use, or long-term smoking)
- Consider temporary hold of immunotherapy

Response to PPI and other risk factors present?

Yes
- Continue PPI treatment
- Address factors contributing to inflammation
- Resume immunotherapy, if held

Follow-up as clinically indicated

No
- Sufficient corticosteroid course to achieve symptom relief followed by taper for total treatment duration less than 30 days
- Re-assess if symptoms recur
APPENDIX A: Modified¹ Common Terminology Criteria for Adverse Events (CTCAE)

<table>
<thead>
<tr>
<th>Gastrointestinal Disorders</th>
<th>Adverse Effect</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diarrhea</td>
<td>Increase of less than 4 stools per day over baseline; mild increase in ostomy output compared to baseline</td>
<td>Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL</td>
<td>Increase of greater than 7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td>Colitis</td>
<td>Asymptomatic; clinical or diagnostic observations only; intervention not indicated</td>
<td>Abdominal pain; mucus or blood in stool</td>
<td>Severe abdominal pain; peritoneal signs</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
</tr>
</tbody>
</table>

¹Modified version includes elements of version 4 and version 5
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SUGGESTED READINGS


DEVELOPMENT CREDITS

This practice consensus statement is based on majority opinion of the Immune Colitis experts at the University of Texas MD Anderson Cancer Center for the patient population. These experts included:

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