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

Disclaimer: This algorithm has been developed for MD Anderson using a multidisciplinary approach considering circumstances particular to MD Anderson’s specific patient population, services and structure, and clinical information. This is not intended to replace the independent medical or professional judgment of physicians or other health care providers in the context of individual clinical circumstances to determine a patient’s care. This algorithm should not be used to treat pregnant women.

**GENERAL EVALUATION**

**PRESENTATION**

Patient presents with new onset of diarrhea\(^1\) one week after immunotherapy initiation and up to 6 months\(^2\) after last dose of immunotherapy\(^3\).

Is diarrhea associated with colitis symptoms\(^4\)?

Yes

Moderate/severe colitis (Grade 2 and above)\(^5\)

Hold immunotherapy and order the following:
- Gastrointestinal (GI) consult
- GI Multiplex PCR panel and fecal CMV PCR\(^6\)
- 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\(^7\), if not drawn within the past 6-12 months

Alternate cause(s) of colitis found?  
Yes

- Initiate appropriate therapy
- Consider Infectious Diseases consult

No

For further assessment/management, see Page 2

Diarrhea alone

For assessment and treatment of diarrhea, see Page 4

**ASSESSMENT**

**TREATMENT**

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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

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CMV = cytomegalovirus
ANA = antinuclear antibodies

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

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Department of Clinical Effectiveness V2
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Evaluation and Management of Suspected Immune-Mediated Colitis/Diarrhea

Other causes for colitis excluded (s) for colitis excluded

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

Yes

Consult Gl

Full colonoscopy and biopsy

Consider EGD and biopsy

No

Refer to assessment and treatment of diarrhea on Page 4

A

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
- Small ulcer < 1 cm, shallow ulcer < 2 mm, and/or number of ulcers < 3
- No infection identified on biopsy

High-risk features:
- Large ulcer ≥ 1 cm, deep ulcer ≥ 2 mm, and/or number of ulcers ≥ 3
- Extensive inflammation beyond left colon
- No infection identified on biopsy

EGD results with confirmed inflammation to stomach and duodenum

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

For upper GI management, see Page 6

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 after completion of corticosteroids

- Corticosteroids 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 (for endoscopy findings and subsequent management, see Page 2)

CLINICAL REMISSION achieved?

- Yes: Continue infliximab or vedolizumab until resolution of inflammation on repeat endoscopy
- No: Resume immunotherapy (PD-1 or PD-L1) after improvement of mucosal inflammation confirmed by repeat endoscopy

SYMPTOM IMPROVEMENT?

- Yes: Consider repeat GI Multiplex PCR panel if more than 1 week after first test
- No: Consider FMT or Consult surgery

ENDOSCOPY FINDINGS

Low-risk features

- Corticosteroids with taper for total treatment duration less than 30 days
- If refractory to corticosteroids after 3 days, consider one dose of infliximab or vedolizumab

Moderate or high-risk features

- Corticosteroids and Start infliximab or vedolizumab within one week of corticosteroid initiation

RESPONSE SEEN ON COLONOSCOPY?

- Yes: Repeat colonoscopy after 3 doses of infliximab or vedolizumab (8-10 weeks after initiation)
- No: Discontinue infliximab or vedolizumab if immunotherapy is not resumed

RESIDUAL INFLAMMATION SEEN ON COLONOSCOPY?

- Yes: Consider repeat colonoscopy if colitis symptoms develop
- No: Consider fecal microbiota transplant (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
PRESENTATION

Mild diarrhea (Grade 1)\(^2\)

- Consider GI infection evaluation (GI Multiplex PCR panel and fecal CMV PCR\(^3\))
- Consider holding immunotherapy temporarily
- Loperamide or diphenoxylate/atropine\(^4\)
- Consider mesalamine 2.4-4.8 grams/day
- Encourage hydration (2-3 liters per day)
- Initiate bland diet

Diarrhea without signs or symptoms of colitis\(^1\)

Moderate and severe diarrhea (Grade 2 and above)\(^2\)

- Hold immunotherapy and order the following:
  - GI Multiplex PCR panel and fecal CMV PCR\(^3\)
  - 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\(^5\), if not drawn within the past 6-12 months

Hold immunotherapy and order the following:

- GI Multiplex PCR panel and fecal CMV PCR\(^3\)
- 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\(^5\), if not drawn within the past 6-12 months
- Consider mesalamine 2.4-4.8 grams/day until culture results return\(^6\)
- Consider hospitalization if inadequate hydration orally

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\(^6\)

Alternate cause(s) of diarrhea found?\(^5\)

- 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)

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)

\(1\) 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 tuberculin; 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

EGD results with confirmed inflammation to stomach and duodenum

- Proton pump inhibitor (PPI) for 2 weeks trial and
- Rule out other factors for inflammation (e.g., 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

No

- Sufficient corticosteroid course to achieve symptom relief followed by taper for total treatment duration less than 30 days
- Re-assess if symptoms recur

Follow-up as clinically indicated

NSAID = non-steroidal anti-inflammatory drugs
APPENDIX A: Modified 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>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 activities of daily living (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>
<td></td>
</tr>
<tr>
<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>
<td></td>
</tr>
</tbody>
</table>

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


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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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