Evaluation and Management of Suspected Immune-Mediated Colitis/Diarrhea

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GENERAL EVALUATION

ASSESSMENT

Hold immunotherapy and order the following:
- Gastrointestinal (GI) consult
- GI Multiplex PCR panel and fecal cytomegalovirus (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 COVID screening if there is suspicion
- 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

Alternate cause(s) of colitis found?

TREATMENT

- Initiate appropriate therapy
- Consider Infectious Diseases consult

Yes

No

For further assessment/management, see Page 2

For recurrent colitis/diarrhea assessment and treatment, see Page 6

- No specific prophylaxis or change in treatment strategy is indicated for management during the COVID pandemic besides the routine precaution
- Diarrhea is defined as the presence of 3 or more unformed stools a day
- On rare occasions, GI toxicities may develop beyond the typical 6 month window
- PD-1 inhibitors (pembrolizumab, nivolumab, cemiplimab), PD-L1 inhibitors (atezolizumab, avelumab, durvalumab), CTLA-4 inhibitor (ipilimumab, tremelimumab)
- Colitis symptoms include abdominal pain, rectal bleeding, and blood or mucus in stools
- Refer to Appendix A for Modified Common Terminology Criteria for Adverse Events (CTCAE)
- 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.
- Screening tests include HIV, T-spot tuberculosis, and hepatitis B and C. Consider screening for fungal infections, if indicated.

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Department of Clinical Effectiveness V3
Approved by the Executive Committee of the Medical Staff on 09/21/2021
Evaluation and Management of Suspected Immune-Mediated Colitis/Diarrhea

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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
  - Consult GI
  - Full colonoscopy and biopsy
  - Consider EGD and biopsy
  - Refer to assessment and treatment of diarrhea on Page 5

- No
  - Other causes excluded

**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

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

For upper GI management, see Page 7

1 Stool: lactoferrin and calprotectin; blood: ESR and CRP
2 Perform colonoscopy and EGD only if ANC > 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
5 Esophageal biopsies are strongly recommended if there is visible evidence of esophageal inflammation on endoscopy

EGD = esophagogastroduodenoscopy
LOWER GI/COLITIS MANAGEMENT

ENDOSCOPY FINDINGS

Low-risk features

- Corticosteroid\(^1\) with taper for total treatment duration < 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 ICI (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)

\(^1\) May consider budesonide as an additional option
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Note: Consider Clinical Trials as treatment options for eligible patients.

LOWER GI/COLITIS MANAGEMENT

ENDOSCOPY FINDINGS

Moderate or high-risk features

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

Symptom improvement after 2 doses of infliximab or vedolizumab?

Yes

- Repeat colonoscopy/sigmoidoscopy after 3 doses of infliximab or vedolizumab (8-10 weeks after initiation)
- Repeat fecal calprotectin at 8 weeks

Repeat fecal calprotectin after second dose

No

Response seen on endoscopic exam or improvement seen in fecal calprotectin from baseline?

Yes

- Residual inflammation seen on endoscopic exam or fecal calprotectin level >116 mcg/g?

- Symptom improvement?

Yes

- Continue infliximab or vedolizumab until resolution of inflammation on repeat endoscopy
- Resume ICI (PD-1 or PD-L1) after improvement of mucosal inflammation confirmed by repeat endoscopy

No

- Consider repeat GI Multiplex PCR panel if more than 1 week after first test
- Consider FMT or Ustekinumab or tofacitinib or Consult surgery

Discontinue infliximab or vedolizumab if ICI is not resumed

No

- Repeat colonoscopy/sigmoidoscopy after 3 doses of infliximab or vedolizumab (8-10 weeks after initiation)
- Repeat fecal calprotectin at 8 weeks

No

Repeat fecal calprotectin after second dose

1 Start steroid taper over 2 weeks after starting infliximab or vedolizumab (total corticosteroid treatment duration should be < 30 days)
2 Consider early repeat colonoscopy/sigmoidoscopy after 2 doses of infliximab or vedolizumab if symptoms persist
3 Fecal calprotectin can be used as an alternative measure to replace repeat endoscopy
4 If resuming ICI continue long-term vedolizumab concurrently
5 Non-formulary at MD Anderson

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PRESENTATION

Diarrhea without signs or symptoms of colitis

Mild diarrhea (Grade 1)

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

Consider GI infection evaluation (GI Multiplex PCR panel and fecal CMV PCR)

Consider holding ICI temporarily

Loperamide or diphenoxylate/atropine

Consider mesalamine 2.4-4.8 grams/day

Encourage hydration (2-3 liters per day)

Initiate bland diet

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)

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 cholestyramine or colesevelam in the absence of endoscopic ulceration

Consider hospitalization if inadequate hydration orally

Alternate cause(s) of diarrhea found?

Yes

Consider Infectious Diseases and/or GI consult as appropriate

No

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

DIARRHEA MANAGEMENT

ASSESMENT/TREATMENT

Mild diarrhea (Grade 1)

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

Moderate and severe diarrhea (Grade 2 and above)

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

Note: Consider Clinical Trials as treatment options for eligible patients.

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, T-spot tuberculosis, hepatitis B and C. Consider screening for fungal infections, if indicated.

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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Note: Consider Clinical Trials as treatment options for eligible patients.

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**Note:** Consider Clinical Trials as treatment options for eligible patients.

### 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

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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 tuberculosis; hepatitis A, B and C panel; and urine *Histoplasma* antigen. Consider screening for fungal infections, if indicated.

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

ASSESSMENT/TREATMENT

EGD results with confirmed inflammation

- Proton pump inhibitor (PPI) for 2 weeks trial and
- Rule out other factors for inflammation (i.e., infections including H. pylori, CMV, HSV, or fungal; recent NSAID use; or long-term smoking)
- Consider temporary hold of ICI

Response to PPI and other risk factors present?

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

No
- Sufficient corticosteroid course to achieve symptom relief followed by taper for total treatment duration < 30 days
- Re-assess if symptoms recur
- Consider corticosteroid with or without biologic therapy for refractory cases
- Consider concurrent biologic therapy if patient is to resume ICI

Follow-up as clinically indicated

HSV = herpes simplex virus
NSAID = non-steroidal anti-inflammatory drugs

1 Vedolizumab is the preferred biologic therapy
APPENDIX A: Modified\(^1\) 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 &lt; 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 &gt; 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
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SUGGESTED READINGS


Continued on next page
SUGGESTED READINGS - continued


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SUGGESTED READINGS - continued


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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