Care Step Pathway - Gastrointestinal Toxicity: Diarrhea and Colitis

Assessment

Look:
- Does the patient appear weak?
- Has the patient lost weight?
- Does the patient appear dehydrated?
- Does the patient appear in distress?

Listen:
- Quantity & quality of bowel movements (e.g., change in/increased frequency over baseline): solid, soft, or liquid diarrhea; dark or bloody stools; or stools that float
- Fever
- Abdominal pain or cramping
- Increased fatigue
- Upset stomach, nausea, or vomiting
- Bloating/increased gas
- Decreased appetite or food aversions

Recognize:
- History of IBD
- Serum chemistry/hematology abnormalities
- Infectious vs immune-related adverse event causation
- Diarrhea with abdominal pain, blood or mucus in the stool and fever
- Peritoneal signs of bowel perforation (e.g., pain, tenderness, bloating)
- Symptoms do not always correlate with severity of disease

Grading Toxicity

Diarrhea (watery bowel movements with any increase in stool frequency over baseline)

Grade 1 (Mild)
- Increase of <4 stools/day over baseline
- Mild increase in ostomy output compared with baseline

Grade 2 (Moderate)
- Increase of 4–6 stools/day over baseline
- Moderate increase of output in ostomy compared with baseline
- Limiting instrumental ADLs

Grade 3 (Severe)
- Increase of ≥7 stools/day over baseline; incontinence
- Hospitalization indicated
- Severe increase in ostomy output compared with baseline
- Limiting self-care ADLs

Grade 4 (Potentially Life-Threatening)
- Life-threatening (e.g., perforation, bleeding, ischemic necrosis, toxic megacolon)
- Urgent intervention required

Colitis (inflammation of the intestinal lining)

Grade 1 (Mild)
Asymptomatic; clinical or diagnostic observation only; intervention not indicated

Grade 2 (Moderate)
Abdominal pain; blood or mucus in stool

Grade 3 (Severe)
Severe abdominal pain; peritoneal signs; medical intervention indicated

Grade 4 (Potentially Life-Threatening)
Life-threatening (e.g., hemodynamic collapse); urgent intervention indicated

Endoscopic Inflammation (Preferred Grading Method)

Mayo Score for Endoscopic Findings

Mayo Score 0
Normal endoscopic appearance

Mayo Score 1
Erythema, mild friability, decreased vascular pattern

Mayo Score 2
Marked erythema & friability, erosions

Mayo Score 3
Spontaneous bleeding, mucosal ulceration

Management

Overall Strategy:
- Rule out infectious, non-infectious, disease-related etiologies
- Endoscopy with biopsy is the gold standard for diagnosis of ICI-related colitis. EGD should also be performed for concurrent nausea, vomiting or epigastric pain
- CT or MRI only if endoscopy is deemed high-risk or contraindicated
- Corticosteroids are 1st line treatment; biologic therapy may be indicated if refractory
- In cases of severe colitis noted on endoscopy, ensure screening labs for hepatitis and TB testing has been performed in case biologic treatment is required
- Assess patient & family understanding of recommendations and rationale
- Identify barriers to adherence

Grade 1 (Mild)
- May continue immunotherapy with close observation and supportive care
  - Maintain adequate oral hydration
- If infectious etiology has been ruled out, antimotility agents such as loperamide or diphenoxylate/atropine can be used as a temporary measure in patients with **diarrhea only**, and no colitis-related symptoms

Grade 2 (Moderate)
- Evaluate for other causes: infectious, pancreatic insufficiency, celiac disease, thyroiditis, concomitant medications (stool softeners / laxatives, magnesium containing agents)
  - Lab: CBC, CMP, TSH, TTG-IgA, total IgA (to evaluate for celiac disease)
  - Send stool sample for *C difficile* testing, culture, and ova and parasite (if recent travel), fecal elastase (to evaluate for pancreatic insufficiency) and lactoferrin or calprotectin (inflammatory stool markers)
- Ensure adequate oral hydration (if necessary, administer IV hydration)
- Refer to GI for endoscopic evaluation
- ICI therapy to be withheld until Grade ≤1 or patient's baseline
- Initiate oral corticosteroids*, prednisone 1-2 mg/kg/day or equivalent (administer IV if unable to tolerate oral therapy due to N/V) until symptoms improve to <G1 and taper over 4-6 weeks (taper period may be reduced if a biologic is added)
- If no improvement is noted within 2 to 3 days or for recurrent symptoms during the steroid taper, consider adding a biologic (infliximab 5 mg/kg or vedolizumab 300 mg) typically at weeks 0, 2, and 6, (though not all doses may be required)
- Taper prednisone, when appropriate over 4 weeks (taper may be reduced)
- In rare circumstances in which the patient cannot be completely tapered off corticosteroids, ICI therapy may be resumed while the patient is on <10 mg prednisone (or equivalent) daily
- Avoid laxatives or stool softeners

Grades 3/4 (Severe or Life-Threatening)
- Evaluate for other causes: infectious, pancreatic, celiac disease, thyroiditis, overuse of stool softeners / laxatives
  - Labs: CBC, CMP, TSH, TTG-IgA, total IgA
  - Send stool sample for *C difficile* testing, culture, and ova and parasite (if recent travel), fecal elastase (to evaluate for pancreatic insufficiency) and lactoferrin or calprotectin (inflammatory stool markers)
- Refer to GI for endoscopic evaluation and co-management
- ICI therapy to be withheld and likely permanently discontinued
- Hospitalize for Grade 4 (consider for Grade 3) and administer IV methylprednisolone (2 mg/kg/day) or equivalent until symptoms improve to Grade 1. Convert from IV methylprednisolone to oral prednisone when appropriate, and taper over 4-6 weeks (taper period may be reduced [e.g. over 2 weeks] if a biologic is also used)
- If no improvement with corticosteroid in 2-3 days, add biologic
- For patients with severe colitis as indicated by ulceration on endoscopic assessment, upfront treatment with biologic should be considered
- Assess for peritoneal signs, perforation (NPO & abdominal x-ray, surgical consult prn)
- Use caution with analgesics (opioids)
- If infliximab not effective, consider vedolizumab 300 mg given IV weeks 0, 2, 6; additional dosages to be determined in consultation with GI
- Supportive medications for symptomatic management:
  - Simethicone when necessary

Management by Endoscopic Findings (Supersedes Management by Grade)

Mayo Score 0 (but evidence of microscopic colitis†)
- Oral budesonide daily x 6 weeks (if stopping ICI), followed by a taper (typically 9 mg to 6 mg x 2 weeks, to 3 mg x 2 weeks) or indefinite maintenance therapy if continuing ICI

Mayo Score 1
- If tolerating oral fluids and bland diet and no systemic symptoms (e.g. fever, dehydration, tachycardia) or electrolyte imbalance:
  - Oral prednisone (0.5 – 2 mg/kg/day) or equivalent followed by taper by 10 mg every 5-7 days after symptoms improve
- If unable to tolerate oral fluids and bland diet, and/or accompanied by systemic symptoms

Mayo Score 2
- IV methylprednisolone 1-2 mg/kg/day divided into two doses every 12 hours

Mayo Score 3
- IV methylprednisolone 2mg IV AND consider initiating biologic (infliximab 5mg/kg or vedolizumab 300 mg, each at weeks 0, 2 & 6). (infliximab is preferred for patients with severe mucosal disease or severe symptoms due to faster response rates).
- If not responsive to infliximab or there is a relative contraindication, initiate vedolizumab

†Microscopic colitis describes a subset of cases in which there is clinical and histologic (microscopic) evidence of colitis but there is no evidence of inflammation on endoscopy nor involvement of the upper GI tract).

Implementation:
- Compare baseline assessment: grade & document bowel frequency and stool consistency
- Early identification and evaluation of patient symptoms
- Grade symptom & determine level of care and interventions required
- Use anti-diarrheals with caution, since overuse in patients with colitis can lead to toxic megacolon and bowel perforation
- Early intervention with lab work and office visit if colitis symptoms are suspected
- Dietary modifications have not been extensively studied; customize the approach to maintain hydration and nutrition
- Diarrhea and colitis may occur together or separately

*Administering Corticosteroids:

Corticosteroid taper instructions/calendar as a guide but not an absolute
- Taper should consider patient's current symptom profile
- Close follow-up in person or by phone, based on individual need and symptomatology
- Corticosteroids may cause indigestion; provide antacid therapy daily as gastric ulcer prevention while on corticosteroids (e.g., proton pump inhibitor or H2 blocker if prednisone dosage is >20 mg/day)
- Review corticosteroid medication side effects: mood changes (angry, reactive, hyperaware, euphoric, manic), increased appetite, interrupted sleep, oral thrush, fluid retention
- Be alert to recurring symptoms as steroids taper down and report them (taper may need to be adjusted)

Long-term high-dose corticosteroids:
- Consider antimicrobial prophylaxis (sulfamethoxazole/trimethoprim double dose M/W/F; single dose if used daily) or alternative if sulfa-allergic (e.g., atovaquone [Mepron®] 1500 mg po daily)
- Consider additional antiviral and antifungal coverage
- If extended corticosteroid use, risk for osteoporosis; initiate calcium and vitamin D supplements
- Patients with asthma or who smoke may have decreased sensitivity to corticosteroids

RED FLAGS:
- **Rapid change in gastrointestinal function, decreased appetite**
- **Bloating, nausea**
- **More frequent stools, consistency change from loose to liquid**
- **Persistent abdominal pain**
- **Fever**

ADLs = activities of daily living; CBC = complete blood count; CMP = complete metabolic panel, CRP = c-reactive protein; EGD = esophagogastroduodenoscopy; ESR = erythrocyte sedimentation rate; ICI = immune checkpoint inhibitor; IBD = inflammatory bowel diseases; NPO = nothing by mouth; PD-1 = programmed cell death protein-1; po = by mouth, TTG-IgA = tissue transglutaminase IgA