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 (query regarding medications/foods eaten); or stools that float
- Mucus in the stool
- Fever
- Abdominal pain or cramping
- Increased fatigue
- Upset stomach, nausea, or vomiting
- Bloating/increased gas
- Decreased appetite or food aversions

Recognize:
- Serum chemistry/hematology abnormalities
- Infectious vs immune-related adverse event causation
- Peritoneal signs of bowel perforation (e.g., pain, tenderness, bloating)

Grading Toxicity

Diarrhea (increased frequency; loose, large volume, or liquidy stools)

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

Grade 5 (Death)

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

Grade 5 (Death)

Management (including Anticipatory Guidance)

Overall Strategy:
- Rule out infectious, non-infectious, disease-related etiologies
- Assess patient & family understanding of recommendations and rationale
- Identify barriers to adherence

Grade 1 (Mild)
- May continue immunotherapy
- Consider loperamide
- Book nursing follow-up call for next business day

<u>Diet modifications (very important):</u>
- Institute bland diet; decrease fiber, uncooked fruits/vegetables, red meats, fats, dairy, oil, caffeine, alcohol, sugar
- Assure adequate hydration

Grade 2 (Moderate)
- Send stool sample for *C difficile* testing, culture, and ova and parasite
- Depending on institutional availability, consider fecal lactoferrin/calprotectin
- Consider gastroenterology consult (for flex sig/colonoscopy/endoscopy)
- Consider abdominal/pelvic CT (w/ contrast)
- Immunotherapy to be withheld until Grade ≤1 or patient's baseline (ipilimumab, pembrolizumab, nivolumab)
- Consider anti-diarrheals: Imodium® (loperamide) or Lomotil® (diphenoxylate/atropine)
- If upper or lower GI symptoms persist >5 days
  - Oral steroids* to be started (prednisone 1 mg/kg/day or equivalent)
  - After control of symptoms, a ≥4-week steroid* taper will be initiated
  - If no response to corticosteroids* in 3 days, treat as steroid* refractory (see specific recommendations under Grades 3/4)
- Immunotherapy to be discontinued if Grade 2 symptoms persist ≥6 weeks (ipilimumab) or ≥12 weeks (pembrolizumab, nivolumab), or for inability to reduce steroid* dose to ≤7.5 mg (ipilimumab) or ≤10 mg prednisone or equivalent (pembrolizumab, nivolumab) within 12 weeks
- Book nursing follow-up call for next business day

<u>Diet modification:</u>
- Institute bland diet low in fiber, residue, and fat (BRAT [Bananas, Rice, Applesauce, Toast] diet)
- Decrease fiber, uncooked fruit and vegetables, red meats, fats, dairy, oil, caffeine, alcohol, sugar
- Assure adequate hydration
- Avoid laxatives or stool softeners
- Advance diet slowly as steroids are tapered,* reduced to low doses and assess for loose or liquid stool for several days or longer
- Steroids* to be tapered slowly over at least 4 weeks

(Moderate) persistent or relapsed symptoms with steroid* taper
- Consider gastroenterology consult for possible reimaging
- IV steroids* to be started at 1 mg/kg/day
- Immunotherapy to be held until ≤Grade 1
- Control symptoms, then ≥4-week steroid* taper
- Recurrent diarrhea is more likely when treatment is restarted

Grades 3/4 (Severe or Life-Threatening)
- Onset:
  - Continued diet modification, anti-diarrheals, and steroid* titration
- Immunotherapy:
  - Grade 3: Pembrolizumab or nivolumab to be withheld when used as single agents; consider resuming when toxicity resolves to ≤ Grade 1
  - Grade 3: Ipilimumab to be discontinued as a single agent and nivolumab discontinued when given with ipilimumab
  - Grade 3 (Recurrent): Permanently discontinue pembrolizumab or nivolumab
  - Grade 4: Ipilimumab and/or PD-1 inhibitor to be permanently discontinued
- Dose of steroids* to be increased (from oral to IV):
  - Steroids* 2 mg/kg/day prednisone or equivalent
- Hospitalization
- GI consultation
- Assess for peritoneal signs, perforation (NPO & abdominal x-ray, surgical consult prn)
- Use caution with analgesics (opioids) and anti-diarrheal medications
- Steroid* taper to include IV to oral transition

<u>Steroid* refractory:</u> (if not responsive within 72 hours to high-dose IV steroid* infusion)
- Infliximab (Remicade®) 5 mg/kg infusion may be considered
- May require ≥1 infliximab infusion to manage symptoms (may re-administer at week 2 & week 6)
- Avoid with bowel perforation or sepsis
- PPD (tuberculin) testing not required in this setting
- Delaying infliximab infusion may have life-threatening consequences
- If infliximab not effective, consider vedolizumab 300 mg

<u>Diet modification:</u>
- Very strict with acute symptoms: clear liquids; very bland, low fiber and low residue (BRAT diet)
- May require complete gut rest
- Advance diet slowly as steroids* reduced to low doses
- Steroids* to be tapered slowly over at least 4 weeks
- **Supportive medications for symptomatic management:**
  - Consider loperamide: 2 capsules at the onset & 1 with each diarrhea stool thereafter, with a maximum of 6 per day
  - Consider diphenoxylate/atropine 1-4 tablets per day
  - Simethicone when necessary

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
- Diarrhea and colitis may occur together or separately

*Administering Corticosteroids:

<u>Steroid taper instructions/calendar as a guide but not an absolute</u>
- Taper should consider patient's current symptom profile
- Close follow-up in person or by phone, based on individual need & symptomatology
- Steroids cause indigestion; provide antacid therapy daily as gastric ulcer prevention while on steroids (e.g., proton pump inhibitor or H2 blocker if prednisone dosage is >20 mg/day)
- Review steroid 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 & report them (taper may need to be adjusted)

<u>Long-term high-dose steroids</u>:
- 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
- Avoid alcohol/acetaminophen or other hepatoxins
- If extended steroid use, risk for osteoporosis; initiate calcium and vitamin D supplements

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; NPO = nothing by mouth; PD-1 = programmed cell death protein-1; po = by mouth