

Care Step Pathway - Gastrointestinal Toxicity: Diarrhoea 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 diarrhoea; dark or bloody stools; or stools that float
- Fever
- Abdominal pain or cramping
- Increased fatigue
- Upset stomach, nausea, or vomiting
- Bloating/increased gas

Recognise:

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

Grading Toxicity

Diarrhoea (increased frequency; loose, large volume, or liquid 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, fluid replacement, and a stool specimen

Diet modifications (very important):

- 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-diarrhoeals: Imodium[®] (loperamide) or Lomotil[®] (diphenoxylate/atropine)
- If upper or lower GI symptoms persist >5 days
 - o Oral steroids* to be started (prednisone 1 mg/kg/day or equivalent)
 - o After control of symptoms, a ≥ 4 -week steroid* taper will be initiated
 - o 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

Diet modification:

- 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 \leq 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:
 - o Continued diet modification, anti-diarrheals, and steroid* titration
- Immunotherapy:
 - o Grade 3: Pembrolizumab or nivolumab to be withheld when used as single agents; consider resuming when toxicity resolves to \leq Grade 1
 - o Grade 3: Ipilimumab to be discontinued as a single agent and nivolumab discontinued when given with ipilimumab
 - o Grade 3 (Recurrent): Permanently discontinue pembrolizumab or nivolumab
 - o Grade 4: Ipilimumab and/or PD-1 inhibitor to be permanently discontinued
- Dose of steroids* to be increased (from oral to IV):
 - o IV methylprednisolone 1-2 mg/kg/day for 3/7 days followed by high-dose oral prednisolone 1-2 mg/kg/day 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

Steroid* refractory: (if not responsive within 72 hours to high-dose IV steroid* infusion)

- IV methylprednisolone 1-2 mg/kg/day for 3/7 days followed by high-dose oral prednisolone 1-2 mg/kg/day or equivalent
- Avoid with bowel perforation or sepsis
- PPD (tuberculin) testing not required in this setting
- Delaying infliximab infusion may have life-threatening consequences
- Diet modification:
 - 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:
 - o Consider loperamide: 2 capsules at the onset & 1 with each diarrhea stool thereafter, with a maximum of 6 per day
 - o Consider diphenoxylate/atropine 1-4 tablets per day
 - o Simethicone-containing products when necessary

Implementation:

- Compare baseline assessment: grade & document bowel frequency and stool consistency, complete a bowel stool chart
- Early identification and evaluation of patient symptoms
- Grade symptom & determine level of care and interventions required
- Use anti-diarrhoeals 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:

Steroid 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 & 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)

Long-term high-dose steroids:

- Consider antimicrobial prophylaxis
- Consider additional antiviral and antifungal coverage
- Avoid alcohol/acetaminophen or other hepatotoxins
- 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

