FIGURE 2

Management of Immune-Related Diarrhea/Colitis[1,4,5,10,13,14,17-19]

Background: It is important to rule out other etiologies that may be responsible for diarrhea, such as *C.difficile* infections. Severe diarrhea has been observed in patients treated with immune therapy. The median time to onset is 6 to 8 weeks for ipilimumab and nivolumab, and 3.4 months for pembrolizumab. Diarrhea/colitis appears to be less frequent with PD-1 blockade than with CTLA-4 blockade.

DIARRHEA/ COLITIS

MANAGEMENT (First rule out infectious causes)

	Description	Referral	Corticosteroids	Supportive Therapy	Immune Therapy
GRADE 1	<4 stools/day above baseline.	Not required.	Not required.	Initiate loperamide£ therapy; maintain oral hydration; consider electrolyte supplementation and dietary modifications.ϕ	Monitor closely and continue immune therapy.
GRADE 2	4-6 stools/day above baseline; abdominal pain, mucus or blood in stool.	Refer to a gastroenterologist for flexible sigmoidoscopy or colonoscopy for persistent grade 2 diarrhea (especially if diagnosis is in question) or any grade 3-4 diarrhea. If any chance of perforation avoid colonoscopy and suggest surgical consult.	Consider starting steroids right away (do not need to wait for consult) or if no improvement after 24 hours of loperamide. Start 0.5-1 mg/kg/day PO prednisone† until resolution to grade 0-1. Then taper over 2-4 weeks if 0.5 mg/kg and over 4 weeks if 1 mg/kg. If no improvement in 72 hours, treat as grade 3-4.	Start loperamide£ and monitor after 24 hours; continue if symptoms improved. Consider prednisone if symptoms worsen or no resolution; give oral/IV hydration; consider electrolyte supplementation and dietary modifications.ϕ	Withhold therapy until grade 0-1 and on prednisone <7.5 mg/day (CTLA-4) or <10 mg/day (PD-1). Consider discontinuation if no improvement within 12 weeks or inability to reduce steroids.
GRADE 3	≥7 stools/day above baseline; incontinence, need for hospitalization for IV fluids ≥24hrs.		Start 1-2 mg/kg/day IV methylprednisolone until improvement, then slow taper over ≥4 weeks. If no response after 3 days, give infliximab 5 mg/kg IV once every 2 weeks* (use with caution in grade 4 due to risk of perforation and avoid if contraindicated).	Admit to hospital and initiate IV hydration. Consider empiric antibiotics as per institutional guidelines for patients who present with fever/leukocytosis. Use opioid analgesics with caution due to risk of narcotic bowel.	Permanently discontinue therapy.
GRADE 4	Grade 3 plus fever, or peritoneal signs consistent with bowel perforation, or ileus; life-threatening.	Suggest surgical consult.			

£ loperamide 4 mg followed by 2 mg q4h or after every loose BM until diarrhea-free for 12hrs (max 16 mg/day)
† or equivalent
ϕRefer to CCO Diarrhea Guidelines: https://www.cancercareontario.ca/en/symptom-management/3151
* If infliximab is contraindicated (possibility of perforation, sepsis, TB, NYHA 3/4 CHF), consider mycophenolate mofetil or other immunosuppressive agents