Immune-related Diarrhoea & Colitis

Gloucestershire Hospitals NHS Foundation Trust

*This treatment guideline is applicable to patients treated with **immune-checkpoint inhbitors (ICIs)**. Onset is usually within 12 weeks from start but can be up to 1 year after the LAST dose. ICIs include PD1/PDL1 inhibitors (**Nivolumab, Pembrolizumab, Atezolizumab, Cemiplimab, Avelumab, Durvalumab**) and CTLA-4 inhibiors (**Ipilimumab, Tremelimumab**). This guideline has been produced jointly by the Oncology and Gastroeneterology specialties.*

Diarrhoea and GI tract inflammation are common side effects of immune checkpoint inhibitor therapy. Although they are typically mild to moderate in severity, if left unrecognised or untreated, they can become life-threatening. Prompt recognition of GI toxicity and, in many cases, rapid institution of corticosteroids (methylpred/pred) or biologic therapy (infliximab) or both is required to reverse these complications.

CTCAE Grading	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life threatening)
Diarrhoea	Increase of <4 stools per day over baseline or mild increase in stoma output	Increase of 4-6 stools per day over baseline or moderate increase in stoma output. Limiting instrumental ADLs	Increase in ≥7 stools per day over baseline or severe increase in stoma output. **Limiting self-care ADLs**	Life threatening consequences e.g haemodynamic collapse
Colitis	Asymptomatic; clinical or diagnostic observation only	Abdominal pain; mucous or blood in stool	Severe abdominal pain, fever, peritoneal signs	Life threatening consequences e.g perforation, ischaemia, necrosis, bleeding, toxic megacolon

Mild (Grade 1)

Investigations:
- Consider repeating baseline bloods
- Consider stool microscopy and culture, C. difficile toxin and ova, cysts and parasites (OCP)

Treatment:
- Encourage oral fluids
- Avoid high fibre and lactose
- Consider loperamide

Actions:
- Telephone assessment within 3 days
- Continue immunotherapy if systemically well

Symptoms: PERSIST (≥5 days) or WORSEN

Symptoms: Resolve or Condition Improving

Actions:
- Taper prednisolone: 40mg, 30mg, 20mg, 15mg, 10mg, 5mg each taken for 3-7 days depending on progress *(or if starting at higher dose, by 10mg every 3-5days down to 10mg daily)*
- Arrange for outpatient follow up / monitoring and fortnightly bloods
- Consider restarting immunotherapy under consultant guidance once symptoms improve to ≤ grade 1 and prednisolone ≤10mg daily

Moderate (Grade 2)

Clinically Assess Patient

Investigations:
- Baseline bloods (FBC, U&E, LFTs, Mg, TFTs & CRP; *random cortisol esp. in ipilimumab-treated patients*)
- Stool microscopy and culture, C. difficile toxin and ova, cysts and parasites (OCP)
- Abdominal XR (consider *urgent* CT abdo/pelvis)

Treatment:
- Oral prednisolone 40mg if average body weight (or 0.5mg/kg/day), consider PPI cover
- Consider IV steroids if oral route not appropriate
- Fluid balance and *electrolyte* replacement

Actions:
- Omit next dose of immunotherapy
- Patient to complete daily stool chart
- Telephone monitoring via helpline

Symptoms: PERSIST (≥3 days) or WORSEN or RELAPSE

Treat as per Grade 3 or 4 (see overleaf)

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Severe or Life Threatening
(Grade 3 or 4)

Admit patient

Investigations:
- Daily bloods (FBC, U&E, LFTs, Mg2+, Bone profile, CRP; *random cortisol esp. in ipilimumab-treated patients*)
- Stool microscopy and culture, C. difficile toxin and ova, cysts and parasites (OCP)
- *Urgent* CT abdo/pelvis
- Urgent inpatient flexible sigmoidoscopy*
  Including 4 x colonic biopsies even if mucosa normal (detail on request)
- Infliximab screen**

Treatment:
- IV methylprednisolone 1-2mg/kg/day, continue for a minimum of 3 days
- Consider PPI cover
- Fluid balance and *electrolyte* replacement

Actions:
- Daily stool chart
- Dietician review
- Hold and consider discontinuation of immunotherapy

Flexible sigmoidoscopy
- *Left colon typically affected, 3-8% have isolated right-sided colitis*
- *Up to 37% may have normal lower GI endoscopic appearances*
- *Macroscopically normal colonic mucosa should still be biopsied because microscopic changes may be seen in 90% with colitis*
- *Colonic ulceration and extensive colitis are associated with corticosteroid-refractory disease and should redcue the threshold for treatment escalation*

Corticosteroids: 2/3 of patients with immune-mediated colitis respond to corticosteroids, 1/3 have no or inadequate response and may need 2nd line therapy

Symptoms: PERSIST (≥3 days) despite IV methylprednisolone OR

Mucosal ulceration or extensive colitis on flexible sigmoidoscopy

*Infliximab 5mg/kg induction regime (if no contraindications)
- Doses at week 0 & 2 and then consider further dose at week 6
- Refer to **infliximab protocol on intranet** for detailed prescribing instructions (Links below)
- Infliximab (gloshospitals.nhs.uk)
- Infliximab | Drugs | BNF | NICE

Refer to gastroenterology if:
- No response to infliximab (or contraindicated)
- Consider vedolizumab, mycophenolate mofetil, calcineurin inhibitor and/or surgical review
- Significant symptoms with no macroscopic or histological colitis OR right-sided colitis on imaging, for consideration of colonoscopy

Symptoms: Resolve or Condition Improving

Actions:
- Convert to oral prednisolone and taper: *70mg, 60mg, 50mg,* 40mg, 30mg, 20mg, 15mg, 10mg, 5mg; each taken for 3-7 days depending on progress
- Arrange for outpatient follow up / monitoring and fortnightly bloods on discharge
- Complete *Medical Day Unit* e-referral on intranet and infliximab paper prescription chart (available in MDU) to arrange subsequent outpatient doses

- Regarding ongoing immunotherapy:
  - **if grade 3 toxicity: permanently discontinue anti-CTLA4 treatment** but can consider resuming anti-PD1/anti-PD-L1 treatments under consultant guidance once symptoms improve to ≤ grade 1 and prednisolone ≤10mg daily
  - **if grade 4 toxicity permanently discontinue immunotherapy**

****Infliximab Screen:** Viral serology incl. HIV, Hep B/C, varicella IgG, TB T-spot, CXR (if CXR or CT chest not already performed)

***Steroid dose**: If other organ system toxicity is present concurrently or develops during steroid reduction (e.g. skin toxicity/ transaminitis/ arthritis etc.) treat with higher steroid dose as per higher grade toxicity*

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