Immunotherapy induced diarrhoea

Immunotherapy administration is associated with immune-related adverse events (irAEs). Gastrointestinal (GI) irAEs are among the most common and although they are typically mild to moderate in severity, if they are left unrecognised or untreated, they can become life-threatening. These toxicities can be managed effectively in almost all patients by using established guidelines that stress vigilance and the use of corticosteroids and other immunosuppressive agents when necessary.

Mild (Grade 1)
- < 4 stools/day over baseline

Management Plan:
- Loperamide, fluid replacement
- Increase frequency of monitoring
- Continue immunotherapy

Symptoms: **Persist** (≥5 days) or **Worsen** or **Relapse**

Symptoms: Resolve or Improve to Mild

Management Plan:
- Initiate corticosteroid taper over 3-6 weeks
- Continue immunotherapy

Moderate (Grade 2)
If any of the following symptoms are present:
- 4-6 stools/day over baseline
- Abdominal pain

Management Plan:
- Omit/defer next dose of immunotherapy
- Review patient
- Loperamide, fluid replacement (prevent dehydration)
- Corticosteroid therapy 1 mg/kg/day oral prednisolone (max. 80mg/day prednisolone)
- PPI cover
- Monitor daily

See section 1.3 Below for further advice

Symptoms: **Persist** (≥5 days) or **Worsen** or **Relapse**

Severe or Life-threatening (Grade 3+4)
If any of the following symptoms are present:
- ≥7 stools/day over baseline
- Abdominal pain
- Fever
- Dehydration
- Blood or mucus in stool

Management Plan:
- Admit patient
- Contact local gastroenterology team for advice/endoscopy
- Commence IV hydration
- High-dose IV corticosteroid therapy (eg. methylprednisolone 2 mg/kg/day or hydrocortisone 200mg iv tds)
- PPI cover

See section 1.1 below for further advice

Symptoms: **Persist** (≥2-3 days of IV steroids) or **Worsen** or **Relapse**

Symptoms: **Persist** (≥5 days) or **Worsen** or **Relapse**

Symptoms: **Persist** (≥2-3 days of IV steroids) or **Worsen** or **Relapse**

Symptoms: Resolve or Improve to Mild

Management Plan:
- Discontinue immunotherapy permanently
- Consider infliximab 5 mg/kg unless contraindicated/perforation/sepsis

See section 1.2 below for further advice

Symptoms: Resolve or Improve to Mild
Managing Immunotherapy Induced Diarrhoea

Gastrointestinal immune related adverse events (irAEs) are generally reported as diarrhoea, defined by frequent and watery bowel movements, and/or colitis, defined by inflammation of the colon. Inflammatory responses may broadly involve the GI tract, including small intestine and upper GI tract, and the symptoms and signs of GI inflammation may extend beyond diarrhoea to include abdominal cramping, nausea, vomiting, GI bleeding, fever, fatigue, dyspepsia, leukocytosis, hypoalbuminemia, and serum electrolyte abnormalities.

As immune-related diarrhoea is a manifestation of inflammatory colitis or enteritis, separate classification of diarrhoea and colitis is somewhat artificial, see table below for grading.

<table>
<thead>
<tr>
<th>Grade 1 Mild</th>
<th>Grade 2 Moderate</th>
<th>Grade 3 Severe</th>
<th>Grade 4 Life-threatening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colitis/ diarrhoea</td>
<td>Asymptomatic, increase &lt; 4 stools per day over baseline</td>
<td>Increase 4-6 stools/day over baseline, abdominal pain, mucous or blood in stool</td>
<td>Increase ≥ 7 stools/day over baseline, severe abdominal pain, change in bowel habit, peritoneal signs, medical intervention indicated</td>
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</tbody>
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Severe colitis should be suspected when the frequency of diarrhoea only meets grade mild to moderate criteria but patients have associated systemic signs and symptoms, including:

- blood per rectum
- cramps
- fever
- nausea
- elevated white blood cell count
- low albumin
- electrolyte abnormalities

1.1 **Severe or life-threatening diarrhoea/colitis:**

Immunotherapy treatment should be permanently discontinued.

**Differential Diagnosis:**
It is important to exclude other causes of diarrhoea in these patients:

- Infection
- Sub-acute obstruction
- Peritonitis
- Perforation
- Constipation with overflow

**Management plan:**
Immediate:
- Admit patient- inform treating oncologist.
- Immunotherapy should be permanently discontinued.
- Contact local gastroenterology team for advice and management. Consider endoscopy to assess for inflammation in bowel.
- Commence IV hydration.
High-dose IV corticosteroid therapy: methylprednisolone 2 mg/kg per day or hydrocortisone 200mg three times daily.

Daily bloods: FBC, urea and electrolytes and CRP.

Investigate aetiology: stool cultures, blood cultures, endoscope, abdominal x-ray, CT abdomen

Regular nursing observations: daily stool chart, fluid balance, twice weekly weight, 4 hourly MEWS assessment.

Dietician review for dietary supplementation.

Consider octreotide subcutaneous 100 mcg – 200mcg three times daily if diarrhoea persistent and is resistant to oral loperamide.

Consider prophylactic antibiotics for opportunistic infections eg septrin, fluconazole.

Remember analgesia can mask acute abdominal symptoms.

**Additionally** for patients who are admitted with severe/life threatening diarrhoea who may require treatment with infliximab, screen for:

- Tuberculosis (Quantiferon Gold or equivalent)
- HIV
- Hepatitis B and C

**Patients that respond to steroids:**

Regardless of improvement, the initial steroid dose should be maintained for $\geq 7$ days, but can be converted to oral administration if the patient is discharged from the hospital. Once symptoms resolve, steroids should be tapered over 3-6 weeks with weekly monitoring for recurrence of symptoms as doses are reduced.

### 1.2 Patients not responsive to steroids:

Patients with severe colitis who have persistent symptoms despite intravenous steroids for $\geq 2$ days should be evaluated for evidence of GI perforation or peritonitis and a repeat endoscopy should be considered. In some patients, doubling the dose of systemic corticosteroids may be sufficient to resolve the symptoms.

Agents such as infliximab at 5 mg/kg or other tumour necrosis factor (TNF)-blocking agents are usually effective when steroids fail. Infliximab therapy can be repeated approximately every 2 weeks, although some patients will require an escalated dose to 10 mg/kg and up to a total of 3-4 doses before the colitis resolves. The steroid taper can be continued after initiation of infliximab.

Inhibition of TNF is associated with the risk of developing serious infectious diseases and difficulty in clearing infections once they have developed. Antibiotic prophylaxis for opportunistic infections should be considered in the rare patient requiring continued immunosuppression $\geq 2$ months.

### 1.3 Moderate diarrhoea:

**Management plan:**

Immediate

- Inform treating oncologist
- Patient must be reviewed
- Omit next dose of immunotherapy
- Oral loperamide 4mg (1st dose) then 2mg 30min before each meal and after each loose stool until 12 hrs without diarrhoea. If continues after 24hrs consider 2-4mg ½ hour before food up to 4 times a day. Max 16mg/day x5 days.
- Increase oral fluid to prevent dehydration, consider adding oral rehyrdation solution (Dioralyte sachets)
- Initiate corticosteroid therapy 1 mg/kg/day oral prednisolone (max. 80mg/day prednisolone)
- PPI cover
- Daily telephone monitoring for assessment of symptoms
- Check FBC, urea and electrolytes and CRP every 3-5 days until symptoms resolve to mild/grade 1
- Obtain stool cultures to exclude infectious causation
- Consider referral to local gastroenterology team for advice and endoscopy
- Consider prophylactic antibiotics for opportunistic infections

**Persistent symptoms MILD ≤ 5 days:**

Begin oral corticosteroid therapy prednisolone 1 mg/kg once daily maximum 80mg daily.
- Investigate aetiology- stool cultures
- Monitor daily

**Persistent symptoms MODERATE ≤ 5 days:**

As mild plus additionally:
- Consider Referal to local gastroenterology team
- Investigate aetiology- blood cultures, consider endoscope
- Check FBC, urea and electrolytes and CRP every 3 days until symptoms resolve to mild/grade 1
- Consider admission for iv steroids

**Improvement in symptoms to mild/grade 1:**

The initial steroid dose should be maintained for ≥ 7 days, once symptoms resolve, steroids should be tapered over 3-6 weeks.

**Patients who develop a recurrence of symptoms:**

Increase dose of cortico-steroids for 5-7 days and a return to a taper schedule over 3-4 weeks may be effective and may obviate the use of anti-TNF agents.

**References:**

https://www.hcp.yervoy.com/pages/remrs.aspx


http://www.medicines.org.uk/emc/medicine/3236/SPC/Remicade+100mg+powder+for+concentrate+for+solution+for+infusion/

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