Guideline for the Management of Systemic Anti-Cancer Therapy (SACT) Induced Diarrhoea in Adult Haematology and Oncology patients.

TARGET AUDIENCE	All clinical staff working within haematology and oncology in secondary care.
PATIENT GROUP	Adult Haematology and Oncology patients within NHSL

Clinical Guidelines Summary

- This guideline describes the pathway for management of Systemic Anti-Cancer Therapy (SACT) Induced Diarrhoea in Adult Haematology and Oncology patients.
- This guideline provides background information and management options and drug prescribing guidance for this patient group.

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Contents

Introduction

Diarrhoea is defined as the frequent passage of loose stools with urgency (or more frequent passage than is normal for the individual). Objectively defined, it is the passage of more than three unformed stools in 24 hours.

Diarrhoea can be a side effect of Systemic Anti-Cancer Therapy (SACT), it is often severe enough to require a dose reduction of, a delay in, or a discontinuation of systemic anti-cancer therapy. It can be debilitating and even life threatening due to fluid loss and electrolyte imbalance, therefore, the impact of severe diarrhoea should not be underestimated.

Cytotoxic SACT drugs that are cited as commonly producing diarrhoea are but not limited to capecitabine, 5-fluorouracil (5-FU), irinotecan, taxanes (doxetaxel and paclitaxel) and combination regimes. However, a large range of other SACT treatments can also cause diarrhoea such as targeted therapies (eg. afatinib, erlotinib, abemaciclib, trastuzumab) and Check-point inhibitor immunotherapy (eg. Pembrolizumab, nivolumab). Diarrhoea as a result of an immune related adverse effect is covered in a separate West of Scotland regional guideline.

The degree and duration of diarrhoea depends on the agent, dose, nadir and frequency of SACT administration. It is not only an inconvenient side effect of cancer treatment, but can be life-threatening if not managed adequately.

Diarrhoea can have a notable effect on performance status and the ability to perform daily activities. Patients may become housebound because of embarrassment, fatigue, dehydration, and abdominal, rectal, and perianal pain, skin abrasion or discomfort, and the fear of needing to defecate suddenly. Diarrhoea may increase the risk of sepsis if the patient is neutropenic.

Points to consider

- Concurrent medication: laxatives, antacids, iron, antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), disaccharide-containing (sugar-free) elixirs, iron, SACT.
- Radiotherapy, particularly when involving the abdomen or pelvis
- Faecal impaction can result in diarrhoea as overflow
- Obstruction: malignant faecal impaction, narcotic bowel syndrome (severe constipation caused by opioid analgesia)
- Malabsorption
- Disease related – pancreatic carcinoma, pancreatic islet tumours, carcinoid tumours
- Concurrent disease, for example diabetes mellitus, hyperthyroidism, pancreatic insufficiency, inflammatory bowel disease such as Crohn's disease, ulcerative colitis, gastrointestinal infection
- Diet for example increase in bran, fruit, hot spices, alcohol
- Current immunotherapy – see guideline for management of immune related adverse effects

Initial Assessment

Take a careful history detailing:

- Document history of presenting symptoms including:
  - Frequency of diarrhoea and information about patient's normal baseline.
  - How long have they had diarrhoea?
  - Timing of the problem
  - Is there an associated temperature (≥38.5°C)?
  - Is there any blood in the stool?
  - Is the patient taking any new medication? If yes, what?
  - Nature of stools including consistency, colour, presence of mucous or blood (brown fluid is likely to be treatment related, yellow/green may indicate that the condition is the result of an infective source and a specimen should be taken)

- Identify SACT treatment prescribed for the patient and establish when the last treatment/tablet was administered?
- Was immunotherapy given? Immunotherapies (eg, nivolumab, pembrolizumab and atezolizumab) have specific guidelines for management of diarrhoea, please refer to information within the **West of Scotland Immunotherapy Guideline for Management of Immune-related Adverse Events**
- Is patient receiving concurrent radiotherapy and when was last treatment? Discuss with radiotherapy team during working hours
- Is the patient participating in a clinical trial? Contact clinical trial team during working hours
- Dietary - has the patient eaten anything that may have caused this condition?
- Has patient recently been constipated?
  Exclude faecal impaction and intestinal obstruction: rectal examination, abdominal palpation, abdominal x-ray may be required to confirm
- Identify toxicity grade as per **Appendix 1**.

Consider infective diarrhoea if:

Refractory grade 2 diarrhoea, recent hospital admission, antibiotics or previous Clostridium Difficile (C.diff) infection:

- Send stool urgently
- If strong suspicion of infective diarrhoea, **withhold anti-diarrhoeal medication until stool result available**
- Stop proton pump inhibitors where possible
- Prescribe antibiotics for treatment of C.diff as per local policy

Consider dehydration if patient reports dry mouth, fatigue, thirst, decreased urine output, headache or feeling dizzy or light headed. Patients with extreme dehydration can also have symptoms of irritability or confusion.

Management

See Appendix 1 for advice on Toxicity grading.

General Advice

- Increase oral fluids (2-3 L per day), avoid caffeinated drinks and alcohol
- Avoid difficult to digest lactose–rich foods such as milk, high-fat foods, raw fruit and vegetables, beans, fibrous vegetables, cereals
- Drink clear fluids and eat simple carbohydrates such as bananas, rice, noodles, white bread, crackers, and gradually reintroduce proteins and then fats as diarrhoea resolves
- Ensure anal area is kept clean and intact by regular washing, use of moist toilet paper or cotton wool (not baby wipes as can contain alcohol) and application of barrier cream (only if the patient is not undergoing concurrent chemo radiotherapy - some barrier creams contain ingredients contraindicated in radiotherapy).
- Stop/ review any medication that may be contributing (e.g. laxatives, domperidone, metoclopramide, magnesium containing antacids).
- **Interrupt / STOP SACT**, including Oral therapy until you have Discussed with the Acute Oncology Team or Oncologist.

If diarrhoea lasts > 48 hours, or if the patient reports symptoms of dehydration or fever, they should be reviewed/admitted as a matter of urgency and admitted to hospital for further management if necessary.

Pharmacological Management

Where there is concern that cause may be infective anti-motility agents should be not be commenced until negative cultures have been obtained.

Table 1: Oral dose of drugs

Treatment Choice	Drug	Indication	Oral Dose
1st line	Loperamide (Capsules)	Anti-motility	4mg initially then 2mg after each loose bowel motion. Maximum 16mg in 24 hours*
2nd line	Codeine (tablets)	Anti-motility	30mg to 60mg every 4 hours as required. Maximum 240mg in 24 hours

** If not controlling diarrhoea rapidly, change loperamide to 2mg four times a day. This can be increased to 4mg four times a day if required.*

Clinical protocols containing drugs that commonly cause diarrhoea often provide specific advice on the management of this side effect.

There is also a detailed **West of Scotland Immunotherapy Guideline for Management of Immune-related Adverse Events**. This guideline contains advice that is specific to this class of medicine with regards to the management of immune related diarrhoea.

Management of diarrhoea due to Irinotecan

Irinotecan can cause both early (acute) and delayed diarrhoea. Early diarrhoea is caused by an acute cholinergic syndrome which can occur shortly after infusion of irinotecan and includes symptoms such as diarrhoea, sweating, abdominal cramping, myosis and salivation.

Management of irinotecan-induced acute diarrhoea:

- Atropine sulphate (250 micrograms subcutaneously) should be administered unless clinically contraindicated and should be used prophylactically for future cycles.

Management of irinotecan-induced delayed diarrhoea:

- At the first loose stool, loperamide should be commenced: 4mg, then 2mg every 2 hours until 12 hours after the last loose stool (up to a maximum of 48 hours) (Note this exceeds licensed dose).
- If diarrhoea lasts > 48 hours, or if the patient reports symptoms of dehydration or fever, they should be admitted immediately to hospital for rehydration and further management, including an infection screen.

The occurrence of severe diarrhoea concomitantly with severe neutropenia is life threatening, requiring immediate admission to hospital and the institution of supportive measures.

Immunotherapy

Immunotherapy is associated with serious immune-related gastrointestinal reactions. Median time to onset of severe or fatal (grade 3-5) reactions is 8 weeks from the start of treatment. However symptoms can occur weeks or months after treatment is discontinued.

Clinical presentation may include diarrhoea, increased frequency of bowel movements, abdominal pain, or haematochezia (bright red blood in stool), with or without fever.

Diarrhoea or colitis occurring after initiation of immunotherapy must be promptly evaluated. Any patient who presents with diarrhoea who is currently receiving immunotherapy or has previously had an immunotherapy should be discussed with the Haematology / Oncology Team as soon as possible.

Please refer to the West of Scotland Immunotherapy Guideline for Management of Immune-related Adverse Events for treatment recommendations.

Appendix 1. Toxicity Grading of Diarrhoea

Toxicity Grading			
Grade 1 Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	**Grade 2** Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	**Grade 3** Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	**Grade 4** Life-threatening consequences; urgent intervention indicated
Systemic Anti-cancer therapy (SACT) including oral chemotherapy should be withheld until discussion with Haematology/Oncology team			
Antimotility drugs not normally required for Grade 1 **If patient also has associated temperature, nausea/vomiting, sore mouth/throat, dizziness, confusion or other clinical concerns – needs medical review/admission**	Initiate loperamide - if ineffective, try codeine. If Grade 2 for >24hours maximal antidiarrhoeal treatment – admit for assessment/admission. Reduce/stop antidiarrhoeal medication after 24 hours free of diarrhoea. **If patient also has associated temperature, nausea/vomiting, sore mouth/throat, dizziness, confusion or other clinical concerns – needs medical review/admission**	Admit patient urgently (unless clinical review suggests no concerns, well hydrated, has not yet had antidiarrhoeals and able to review patient daily). History to include other chemotherapy toxicities (risk of damage to rest of GI tract and skin –manage nausea/ mucositis /sepsis/hand-foot syndrome according to local guidelines). Assessment of fluid balance status (BP, pulse etc) and signs of systemic infection. **Fluid resuscitation and electrolyte replacement where indicated.** Stop **ACE-inhibitors/ Angiotensin-II inhibitors /diuretics/ NSAIDs /metformin.** Daily bloods (U&Es, FBC, CRP, magnesium, albumin, blood cultures if signs of systemic sepsis), NEWS, cumulative fluid balance. Stool sample (send for urgent culture, C diff toxin and viral screen - discuss with Microbiology). Consider abdominal X-Ray to exclude ileus/ obstruction/ perforation /megacolon. Dietician review if appropriate	

References/Evidence

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Appendices

1. Governance information for Guidance document

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