Management of Systemic Anti-cancer Therapy (SACT) - Induced Diarrhoea

Please note for immunotherapy-associated diarrhoea, please refer to Immunotherapy Toxicity Management guidelines

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Definition

Increase in stool frequency (relative to patient's baseline) and/or loose bowel movements

Objective measure = passage of > 3 stools over baseline in 24hr or mild increase in ostomy output compared to baseline

Practice point: patients' definition of diarrhoea may vary so important to clarify during initial assessment

Red flags: abdominal pain, mucus or blood in stools.

Importance

Common side effect of treatment.

Impacts greatly on QoL and may even be life-threatening.

May lead to treatment delays, dose reduction, hospital admission and even death.

Risk of serious illness significant in those who are neutropenic.

SACT agents most frequently associated with diarrhoea:

Capecitabine/Fluorouracil (5-FU)
Taxanes e.g. Docetaxel, Cabazitaxel
Irinotecan – see appendix 1
Tyrosine Kinase Inhibitors (TKIs) – see appendix 2
Immunotherapy – see appendix 3
Lenalidomide & Bortezomib – Bile Salt malabsorption diarrhoea see appendix 4
CDK4/6 inhibitors e.g. Abemaciclib, Ribociclib
AKT inhibitors e.g. Capivasertib
FGFR Inhibitors e.g. Erdafitinib
Antibody–Drug Conjugates e.g. Sacituzumab govitecan, Enfortumab vedotin

Initial Evaluation

Grade according to stool frequency/stoma output (see Table 1)

Adverse features? (see Box 1)

Which chemotherapy regime and when was last treatment?

Document result of DPD testing (if applicable – see Box 2)

Diarrhoea with previous cycles?

Any other chemotherapy toxicities, e.g. mouth ulcers, mucositis, nausea/vomiting, red hands/feet?

Consider other causes (see Box 3)

Any recent RT with fields including GI tract? Consider possibility of Bile Salt malabsorption diarrhoea if not responding to standard treatment, see appendix 4

Risk factors for C. diff? – recent use of antibiotics, use of PPI, recent hospitalisations, personal history of C. diff

Risk factors for infective diarrhoea? – potential food culprit (e.g. takeaway), travel history, infective contact

Table 1: Diarrhoea assessment criteria (CTCAE grading)

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhoea (without stoma)	Increase of <4 stools per day over baseline	Increase of 4-6 stools per day over baseline	Increase of ≥ 7 stools per day over baseline; Hospitalisation	Requires intensive support or hemodynamic collapse
Diarrhoea (with stoma)	Mild increase in ostomy output compared to baseline	Moderate increase in ostomy output compared to baseline. Not interfering with daily living activities	Severe increase in ostomy output compared to baseline. Interfering with daily living	

Box 1

Adverse features? Any of the following:

Abdominal pain/cramping
Incontinence
Bloody diarrhoea
Nocturnal diarrhoea
Fever / sepsis
Neutropenia
Nausea & vomiting
Dehydration
Decline in performance status

Box 2

DPD testing

DPD (dihydropyrimidine dehydrogenase) is an enzyme involved in the clearance of fluoropyrimidines (i.e. 5-FU, Capecitabine).

DPD deficiency causes prolonged drug exposure and increased risk of toxicity.

This enzyme deficiency is usually caused by genetic mutations in the DPYD gene.

Pre-treatment testing for DPYD variants is now done routinely in order to identify those at high risk of toxicity. Result should be checked on WCP and documented on ChemoCare

N.B: whilst the most common DPYD variants can be detected, there are rare DPYD variants not covered by routine testing. Consider DPD deficiency in patients treated with 5FU products who present early with severe diarrhoea +/- mucositis.

Box 3

Imaging

- **When?** If any signs peritonism OR if symptoms not settled within 48hr
- **What?** AXR or proceed straight to CT if adverse features – discuss with senior if unsure
- **Why?** To assess extent of bowel involvement, exclude neutropenic enterocolitis, detect complications (e.g. perforation, abscess, enterocolitis, malignant intestinal obstruction)

Box 4

Other causes to consider

- Subacute obstruction or constipation with overflow
- Infective diarrhoea, in particular C. diff
- CMV colitis
- Typhilitis (inflammation of the caecum)
- Steatorrhea (in pancreatic or biliary malignancy)
- Bile salt malabsorption related (Lenalidomide, Bortezomib, TKIs)
- Hypersecretion of 5-HIAA (carcinoid tumours)
- Small intestinal bacterial overgrowth (SIBO)
- Other GI disease e.g., diverticular disease, IBD
- Medications e.g., laxatives, prokinetics
- Enteral feeding
- Radiotherapy induced enterocolitis
- Immunotherapy induced colitis
- Travellers' diarrhoea

Management

Those with G1-G2 diarrhoea (no adverse features): usually can be managed at home

Those with G3-G4 generally need admission

- Observations: Calculate and monitor NEWS score
- Investigations: Urgent FBC, U&Es, Mg2+, LFT, CRP, phosphate. C diff screen and stool culture ('Microbial investigation - faeces' request on WCP – need to specify if you would like to include norovirus screen). Consider blood gases if severe diarrhoea/possible acidosis.

General points

Withhold SACT

IP/OP monitoring and appropriate fluid resuscitation – NB. those with severe diarrhoea may lose up to 4-6L/day

Electrolyte replacement – see **individual guidelines on COIN**

Medication review – stop ACEi/diuretics/NSAIDs/laxatives/pro-kinetics. Avoid domperidone and metoclopramide anti-emetics.

Consider if absorption of regular medication (e.g. anti-epileptics) might be affected and if alternative routes of administration or closer monitoring are required.

Send stool culture

Practice point:
Oncology patients: do not delay starting anti-diarrhoeals while awaiting stool culture results unless high suspicion of infective diarrhoea but consider mega colon first.

Haematology patients: negative infection screen is required prior to starting anti-diarrhoeals

If the patient has a high output ileostomy or colostomy, higher doses of loperamide may be needed– discuss with a senior.

If possible, ask patient to keep own stool chart (as this is often most accurate) / use Bristol stool chart (appendix 5)

Seek specialist advice early for patients not responding to treatment.

If concern this is an acute abdomen, arrange imaging and discuss with surgical SpR. Patient should be NBM pending surgical review.

If **neutropenic:**
Monitor for pyrexia – if febrile, treat as per **neutropenic sepsis policy**
Consider antibiotics – check guidelines
https://nhswales365.sharepoint.com/sites/SBUClinicalPathways/SitePages/Antimicrobial.aspx

G1-2 (uncomplicated)

Initial Management

- Start loperamide – 4mg STAT then 2mg every 2-4hr. Max 16mg/24hr
- Increase PO fluids (2-3L/day)
- Dietary Modification (small frequent meals, oral rehydration solution)

Reassess after 12-24hrs

If improving

- Continue current management
- Continue anti-diarrhoeals for 12-24hr after resolution of diarrhoea

If static

- Review/stop SACT
- Increase loperamide to maximum dose (2mg every 2hr)
- Add codeine phosphate 30-60mg QDS
- Consider budesonide – 9mg OD for 3-5/7

Reassess 24-48hrs later

Reassess as above
If not improving, consider dietician review and seeking gastroenterology advice

Progressed to G3-4

G3-4 (or grade 1-2 with adverse features)

Initial Management

- Admit to hospital for medical review
- Start I.V. fluids and electrolytes
- Calculate and monitor NEWS score
- Arrange:
  - FBC, U&Es, CRP, Lactate, Mg2+
  - Abdominal X ray +/- CT if adverse features (see Box 1)
  - Microbiology (stool MCS, C.diff.) – 'Microbial investigation – faeces' on WCP
- Discontinue SACT until symptoms resolve
- Start loperamide – 4mg STAT then 2mg every 2-4hr. Max 16mg/24hr
- If already taking loperamide > 24hr in community, add codeine phosphate 30-60mg QDS and consider Octreotide infusion as below

Reassess after 12-24hrs

If improving

- Continue current management
- Continue anti-diarrhoeals for 12-24hr after resolution of diarrhoea

If not improving

- Increase loperamide to maximum dose (2mg every 2hr)
- Add codeine phosphate 30-60mg QDS
- Start octreotide via continuous sub-cut infusion (syringe driver) 600micrograms/24h.
- Dietician review for nutritional assessment and consideration of TPN

Reassess 24-48hrs later

Reassess as above
If not improving, could increase octreotide (titrate up to 1200micrograms/24 hours) Contact gastroenterology for advice

Appendix 1 – Management of Irinotecan- induced diarrhoea

The onset of diarrhoea maybe acute (<24 hours of administration) or delayed (>24 hours of administration).

Acute: cholinergic syndrome occurs during administration of Irinotecan and can be controlled by giving *Atropine 300 micrograms SC* during administration, this is included on the chemotherapy prescription. Should the syndrome develop after administration a further dose can be given.

Delayed: the risk is increased in patients:

- Previous abdominal/pelvic radiotherapy.
- Patients with baseline hyperleukocytosis
- Patients receiving concurrent 5-FU or capecitabine
- Performance status ≥ 2
- Women

As soon as the first liquid stool occurs the patient should:

- Drink large volumes of water
- Take loperamide 4mg immediately
- Take loperamide 2mg **every 2 hours** for at least 12 hours and for 12 hours following the last liquid stool. Max at these high doses for no more than consecutive 48 hours because of risk of paralytic ileus, nor for less than 12 hours.

Admit to hospital if:

- Persistent diarrhoea for >48 hours despite high dose loperamide therapy
- Severe diarrhoea (requiring intravenous hydration)
- Diarrhoea with fever
- Concomitant vomiting

In patients who experienced severe diarrhoea, a reduction in dose is recommended for subsequent cycles

Appendix 2 – targeted therapies

Tyrosine Kinase Inhibitors (TKIs) may also cause diarrhoea. Please see below list of those commonly used (note this list is not exhaustive):

- Afatinib
- Axitinib
- Bosutinib
- Cabozantinib
- Crizotinib
- Dacomatinib
- Dasatinib
- Erlotinib
- Gefitinib
- Imatinib
- Lapatinib
- Lenvatinib
- Neratinib
- Nilotinib
- Osimertinib
- Pazopanib
- Ponatinib
- Regorafenib
- Sorafenib
- Sunitinib
- Vandetanib

Appendix 3 – Immunotherapy Drugs

Not all non-cytotoxic drugs are classed as “immunotherapy”; this is a specific group of drugs that produces a range of side effects unique to them

Below are examples of checkpoint inhibitor immunotherapy drugs but the list may not be exclusive and if in doubt check the product licence or seek further advice. Please refer to Management of Toxicities from Immunotherapy guidelines available on COIN for management of diarrhoea in immunotherapy patients.

- Atezolizumab
- Avelumab
- Cemiplimab
- Dostarlimab
- Durvalumab
- Ipilimumab
- Nivolumab
- Pembrolizumab
- Relatlimab
- Tremulimumab

Appendix 4 – Management of Bile Salt malabsorption diarrhoea

Characterised by watery diarrhoea with urgency in most patients and faecal incontinence in more than half of patients. Lenalidomide causes BAD in 20% of patients a median of 4 months after being prescribed. It is severe in 73% of patients and can rapidly evolve into a life-threatening hypokalaemia and severe AKI.

It responds in majority of cases to treatment (see below). It can also occur, less frequently, with bortezomib based therapy.

Diagnosis

It should be considered in any patient with Multiple Myeloma on lenalidomide or bortezomib who develops unexplained severe diarrhoea or those with history of prior pelvic RT who are not responding to standard treatment.

Diagnosis can be established by non-invasive selenium homocholic acid taurine (SeHCAT) scan OR adequate response to bile acid binders such as colesevelam.

Be aware of false positive SeHCAT results if the patient is no better despite intensive therapy

Treatment

1. Reduce fat intake to 20% of total calories
2. Start one of:
    - Cholestyramine 4-8 g with breakfast to bind bile produced overnight. This will bind 75% of bile acids and reduce impact on absorption of other drugs taken during the day and fat-soluble vitamin deficiencies, for further advice contact Gastroenterology.
    - Colesevelam up to **6 x 625 mg tablets daily** (1.25–3.75 g), in **2–3 divided doses.** It is the only EMA licenced product for this indication. Consider starting at one tablet a day for a week, then 2 in week 2 and so on up to week 6. They also need annual monitoring of fat-soluble vitamins and cholesterol if they remain on the medication long term.


Bile acid malabsorption diarrhi


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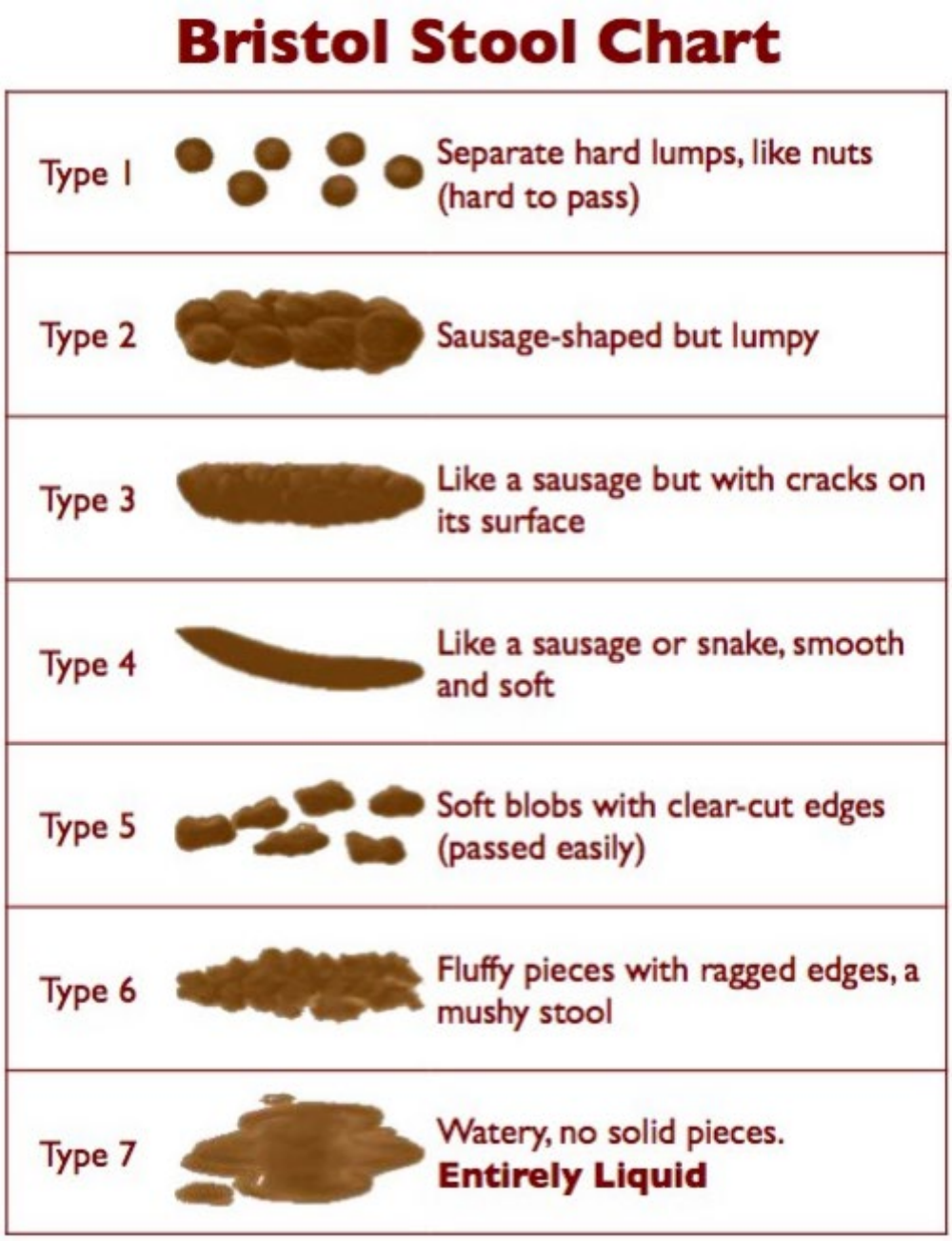
Appendix 5: Bristol Stool Chart



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Swansea Bay University Health Board

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