

# Guidelines for the Management of Systemic Anti-cancer Therapy (SACT) Induced Diarrhoea in out-patients

The purpose of this guidance is to make recommendations for the prevention and treatment of out-patient SACT induced diarrhoea and includes those caused by '*classical or* conventional' cytotoxic agents and '*Targeted*' Therapies, such as tyrosine kinase inhibitors.

Please refer to separate guidelines for diarrhoea induced by:

- Immunotherapies
- Radiotherapy (+/- combined with chemotherapy)
- Or
- Management of capecitabine induced diarrhoea requiring hospital admission

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Prior to commencing any new treatment, baseline bowel movements/stoma output should be documented and patients provided with advice on maintaining and maximising health during treatment through adequate fluid intake, healthy diet and use of anti-diarrhoeal drugs. Prompt reporting of side-effects can reduce the incidence and severity of diarrhoea, as early treatment may prevent hospital admission.

## Definition:

SACT induced diarrhoea is classified as:

- an increase of at least 2 to 3 or more stools per day over baseline, **and/or**
- causing waking at night, **and/or**
- an increase in loose, watery stoma output compared with before treatment, (see Bristol Stool Chart, type 5-7, appendix i).

**A once daily stool (during the day), no matter how soft is not diarrhoea.**

## Impact on Patient:

Diarrhoea may have a profound impact on a patient's quality of life and their physical and emotional well-being. Patients not only have to cope with increased frequency of bowel movement but may have abdominal pain, cramping, anal/perianal skin breakdown. Food aversions may develop or patients may stop eating altogether as they anticipate subsequent diarrhoea following intake. Consequently this may lead to weight loss and malnutrition. Fatigue, sleep disturbances, feelings of isolation and depression are all common consequences of those experiencing diarrhoea.

Uncontrolled diarrhoea may necessitate treatment interruptions, dose reductions or stopping treatment prematurely, which could compromise treatment efficacy or result in death.

Accurate baseline data is required so that a basis for comparison exists and it can be determined whether any symptoms are treatment related.

## SACT Induced Diarrhoea:

SACT induced diarrhoea is caused by a combination of mechanical and biochemical disturbances stimulated by chemotherapeutic effects on the bowel mucosa. Most anti-cancer drugs are anti-proliferative agents and are toxic to dividing cells or they prevent cells division. These drugs are also toxic to other normal proliferating tissues of the body such as the gut mucosa. When epithelial integrity is disturbed, the mucosa becomes inflamed, oedematous and the absorptive surface area is decreased.

## SACT Agents Causing Diarrhoea

Nearly all cytotoxics have the potential to induce diarrhoea. The drugs listed below commonly cause diarrhoea and require some specific management.

<b>Classic Chemotherapy</b>	5-Fluorouracil (5FU), especially continuous.	Increased risk by addition of leucovorin.  <b>If diarrhoea is grade 2 or above, treatment may be interrupted until symptoms have recovered or resolved to grade 1, (CTC grading, page 7), IF SYMPTOMS NOT RESOLVING OR WORSEN REFER TO MANAGEMENT OF SEVERE CAPECITABINE INDUCED DIARRHOEA.</b>
	Capecitabine	Severe diarrhoea and/or mucositis and/or palmar-plantar in the first cycle may be due to a deficiency of an enzyme called dihydropyrimidine dehydrogenase, (known as DPD deficiency). It is a genetic disorder and DPD is required for the metabolism of active 5FU to inactive metabolites.
	Irinotecan	Following treatment with irinotecan, onset of diarrhoea may be acute (< 24 hours after administration) or delayed (> 24 hours after administration).  <b>Acute - Cholinergic syndrome</b> occurs during or within 24 hours of irinotecan administration. It is prevented or controlled by atropine 250micrograms subcutaneously at the time of irinotecan administration. Should the syndrome develop a further dose of atropine may be given.  <b>Delayed</b>  Patients must be made aware of the risks of delayed diarrhoea which can occur more than 24 hours after irinotecan administration for duration of cycle.  The risk of diarrhoea is increased in patients who have had previous abdominal / pelvic radiotherapy, who are also receiving 5-FU or capecitabine and have a performance status > 2.
	Actinomycin D Cisplatin (at high doses) Cladribine Dacarbazine Daunorubicin Docetaxel Hydroxyurea	Gemcitabine Idarubicin 6-Mercaptopurine Methotrexate Mitomycin C Oxaliplatin Paclitaxel
<b>Small Molecule Antibodies</b>	Ipilimumab Nivolumab Pembrolizumab	<b>Requires prompt specialist management by an oncologist experienced in its use and according to the TVSCN ipilimumab protocol and SmPC.</b>
	Rituximab	Bowel perforation or new-onset ulcerative colitis or exacerbation of pre-existing colitis has been reported.
	Cetuximab	Increased risk of diarrhoea when cetuximab combined with oxaliplatin and capecitabine. Consult TVSCN protocol, consider dose reduction and discuss management with patient's treating consultant.
	Atezolizumab Durvalumab	Cause diarrhoea, but severe diarrhoea is rare
<b>Tyrosine Kinase Inhibitors</b>	Afatinib Axitinib Bosutinib Ceritinib Crizotinib Dacomitinib Dasatinib Erlotinib Gefitinib Lapatinib Nilotinib Osimertinib Pazopanib	May start within 2-3 days of starting treatment.  As these drugs are long-term treatment, it is unlikely that symptoms can be resolved completely and the aim of management is to maintain diarrhoea at acceptable/controllable levels for the patient.  Grade 3 affects up to 28-66% patients  Check regimen for dose reductions / withhold drug

	Sorafenib Sunitinib	
<b>Cyclin-dependent Kinase Inhibitor</b>	Abemaciclib Palbociclib Ribociclib	Cause diarrhoea. Check regimen for appropriate dose reductions / withholding drug.

This is not an exhaustive list and as new drugs are licensed, each SPC will need to be checked.

### **Patient Education:**

Before starting a SACT with the potential to cause diarrhoea, baseline bowel movements/stoma output should be determined. Patients do not need to modify their diet in anticipation of possible diarrhoea, they can continue to eat a full, unrestricted diet, but must be educated of the potential and what action to take should they experience diarrhoea, with emphasis that early treatment may prevent premature discontinuation of the treatment or hospitalisation. If taking laxatives, patients should be advised that they may need to decrease dose or temporarily stop these whilst on treatment.

Patients should be given hospital/triage details and advised to report immediately any of the following symptoms associated with diarrhoea:

- Fever, Abdominal cramps, pain or bloating (especially if receiving vinca-alkaloids),
- Nausea/vomiting, Weight loss,
- Dizziness, increased fatigue or weakness,
- Sudden rapid or irregular heartbeat,
- Blood in stool,
- Inability to drink an adequate amount of fluids for >12 hours,
- Dark coloured urine or inability to urinate for 12 hours or more,
- Following cycle 1 5FU, if patients have mucositis +/- palmar plantar, consider DPD deficiency.

**In the event of diarrhoea, patients should be given the following non-pharmaceutical and pharmaceutical advice:**

### **Non Pharmaceutical Advice:**

- Drink 8-10 large glasses of clear fluids per day; ensure it is not all plain water but fluids containing salts/sugars e.g. clear soup, noncarbonated soft drinks.
- Consider an oral rehydration solution as part of fluid intake.
- Eat frequent small meals as tolerated (e.g. bananas, white rice, white bread, noodles, plain pasta, apple sauce, white meat, scrambled egg).
- Stop Lactose-containing products and high-osmolar dietary supplements, i.e. milk based drinks, cheese.
- Avoid spices, high fibre foods, whole grain breads & cereals, raw vegetables, gas forming foods including beans, cabbage, broccoli, or carbonated drinks, high fat food (e.g. fried), caffeine, alcohol and fruit juices.
- Instruct patient to record the number of stools and when to re-report symptoms.
- Use of Barrier creams to protect the skin in anal/perianal region, (if patient is having radiotherapy, the creams must not contain zinc nor metallic ions).
- If required the patient may require a referral to a dietician who can offer advice on a low fibre diet and high fluid intake.

## Treatment - Simple Pharmaceutical Measures

(Loperamide can be bought over the counter, patients are able to take at home & increase dose if required)

	Indication	Mode of Action	Dosing	Administration	Caution
<b>Loperamide</b>	First line treatment of diarrhoea	Synthetic opiate that has direct effects on smooth muscle, which decreases motility & increases anal sphincter tone; minimum absorption and no central activity.	Initially 4mg, followed by 2mg with each loose stool or every 2-4hrs, maximum 16mg per 24hours.  At night, 4mg every 4 hours.  Ensure loperamide is administered until 12hrs post last loose stool.  For increased physiological benefit take 30min before eating four times daily to slow gastrocolic reflex.  NB. For patients with an ileostomy/stoma loperamide dosing is lower, 2mgs QDS, increase to maximum 12mg/24hrs. Often needs to be taken routinely before meals - contact stoma nurse for specialist advice and management.	Oral tablets / Capsules or liquid preparation; the latter might have faster onset of action and allows for finer dose adjustments than tablet / Capsule; effectiveness is increased substantially if taken 30min before food	Side-effects: Constipation, flatulence, vomiting & headache.  Aggressive dosing risks paralytic ileus.

## Signs and Symptoms:

### CTC Grade of Diarrhoea

	Grade 1	Grade 2	Grade 3	Grade 4
<b>STOOLS</b>	Increase of < 4 stools/day over baseline	Increase of 4-6 stools/day over baseline, Nocturnal, not affecting Activities of Daily Living (ADL)	Increase of 7-9 stools/day, incontinence, Hospitalisation, interfering ADL, hospitalisation	Greater than 10 stools/day over baseline, bloody stool, life threatening, haemodynamic collapse.
<b>STOMA OUTPUT</b>	Mild increase in output compared to baseline	Moderate increase in stoma output compared to baseline, not interfering with ADL	Severe increase, effects as above	
<b>SYMPTOM</b>		Moderate cramping	Severe cramping	Need for parenteral fluid support

### Classification of Diarrhoea

<b>Uncomplicated</b>	CTC grade 1 or 2 with no complicating symptoms (as detailed below).
<b>Complicated</b>	<p>CTC grade 3 or 4 +/- complicating symptoms as listed below  <b>OR</b>            CTC grade 1 or 2 <b>with</b> one or more of the complicating symptoms as listed below <b>and/or</b> not responding to maximum dose loperamide+/-codeine, i.e.</p> <div> <div>           Abdominal cramps,            Nausea / vomiting, Mucositis,            Weakness,            Fever / sepsis,            Dizziness,            Dark coloured urine +/- reduced volume,            Palmar/plantar, Mucositis (especially post cycle 1, consider DPD, neutropenia will follow quickly)         </div> <div>           Reduced oral intake &gt;12 hrs,            Reduced performance status,            Weight loss,            Neutropenia,            Rapid/Irregular heartbeat         </div> </div>

### Assessment of Patient Presenting with Diarrhoea:

Stools – frequency & composition, blood, nocturnal, incontinence (CTC grade and Bristol Stool Chart) compared to baseline bowel habit.

- Associated symptoms – Abdominal cramps, Reduced oral intake >12 hrs, Nausea / Vomiting, Mucositis, Reduced Performance Status, Weakness, Weight loss, Fever / Sepsis, Neutropenia, Dizziness, Dark coloured urine +/- Reduced Volume, Rapid/Irregular heartbeat, Palmar/Plantar, Mucositis (especially post cycle 1, consider DPD deficiency, as neutropenia will follow quickly)
- Intra-abdominal and/or pelvic primary or metastatic disease, eg colorectal, abdominal lymphoma,
- Intra-abdominal and/or pelvic surgery,
- Cancer treatment – chemotherapy +/- radiotherapy within 21 days,
- Ascertain amount & frequency of loperamide +/- codeine being taken,
- Other medication – especially antibiotics, diarrhoeogenics – bulking agents or softeners, antacids that contain magnesium as they can increase diarrhoea, Proton Pump Inhibitors (PPI's),
- Dietary profile – to identify diarrhoea enhancing foods,
- Recent hospital admissions, Age.

### Management:

#### Uncomplicated Diarrhoea (Grade 1 or 2, without any complicating symptoms)

Patient can stay at home,

Commence or increase simple Pharmaceutical measures (page 6).

Advise patient re Non Pharmaceutical measures (page 6 & 10).

Record number of bowel movements, composition and daily weight.

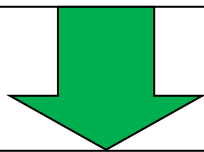
Re: Anti-cancer treatment:

- grade 1 diarrhoea, may continue anti-cancer treatment,
- grade 2 diarrhoea, continue cytotoxic drug whilst increasing to maximum dose of loperamide,
- grade 2 diarrhoea not responding to maximum dose loperamide, stop chemotherapy drug until diarrhoea/other symptoms have resolved, only restart chemotherapy drug when advised by the cancer medical team,
- Ensure medical team are informed.

**Flowchart for Management of Out-Patient Chemotherapy Induced Diarrhoea**

**PATIENT ASSESSMENT (see page 8 & 9)**

- **Stools:** Current Bowel symptoms i.e. Frequency (CTC grade), composition, blood, nocturnal, incontinence, compared to baseline.
- **Complicating symptoms:** Fever (? risk of Neutropenia), Blood in stool, Weakness and Reduced performance status, Reduced oral intake >12 hours, Abdominal cramps, Nausea / Vomiting, Weight Loss, Mucositis, Palmar/Plantar, Rapid/Irregular heartbeat, Dizziness, Dark coloured urine
- **Anti-cancer Treatment:** Recent SACT, Radiotherapy or bowel surgery,
- **Anti-diarrhoeal medication:** Taking loperamide +/- codeine, dose & frequency,
- **Other medications:** Antibiotics, laxatives, antacids with magnesium, PPI's
- **Dietary profile:** Diarrhoea enhancing foods,
- **Any recent hospital admissions, elderly**



**Uncomplicated Diarrhoea (see page 7)**

**Grade 1 or 2, (i.e. increase in bowel movements of up to 6 stools per day or moderate increase in stoma output over baseline +/- moderate cramping, not affecting ADL (see page 7)**

Patient can stay at home,

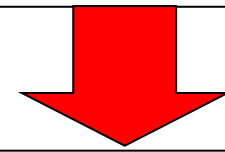
Advise as per 'Non Pharmaceutical Advice' and Simple Pharmaceutical Measures (page 6).

Ask patient to document stool frequency and re-contact if worsening or develops any complicating symptoms (page 7).

If Grade 2 & not responding to maximum dose of loperamide, stop SACT, until resolution to Grade 1.

Liaise with patient's medical team, refer to protocol and consider dose reduction.

Reassess as required until diarrhoea resolved or until is manageable for the patient.










**Complicated Diarrhoea (see page 7) / Grade 3 or 4 Diarrhoea**

**(i.e. increase of 7+ stools per day/severe increase in stoma output over baseline, interfering with ADL) OR Grade 1 or 2 with one or more of the following Complicating Symptoms +/- not responding to maximum dose loperamide (see page 7):**

**Refer to appropriate guidelines**



## Bristol Stool Chart

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on its surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges (passed easily)
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces. <b>Entirely Liquid</b>



**Differential Diagnosis:** needs to be considered when managing chemotherapy induced diarrhoea in the out-patient setting.

**NB:** If patients are within 30 days of receiving a chemotherapy drug and require assessment or attend the emergency department, triage +/- require hospital admission, refer to the appropriate protocol for:

- Management of severe capecitabine induced diarrhoea
- Management of Immunotherapy induced diarrhoea
- Management of radiotherapy induced diarrhoea (+/- combined with chemotherapy)

- Infective episodes / food poisoning – including **clostridium difficile** (refer to Trust guidelines).
- Subacute bowel obstruction (colonic tumour in situ, lymphoma in bowel, post-surgical adhesions),
- Constipation with overflow,
- Hypersecretion of 5HIAA, as in Carcinoid cancers,
- Biliary obstruction,
- Steatorrhoea in biliary and pancreatic malignancies,
- Malabsorption syndromes,
- Overdose of fibre, check patient's diet,
- Other medications (some antacids contain magnesium, Proton Pump Inhibitors –PPI's),
- Graft versus Host disease in patients post-transplant,
- Non-malignant bowel conditions e.g. diverticulitis, appendicitis, ulcerative colitis, etc.

#### References:

Andreyev J, Ross P, Donnellan C, Lennan E, Leonard P et al (2014) *Guidance of the management of diarrhoea during cancer chemotherapy*. Lancet, September, Vol 15, 10, e447-460