NHS England

Management of Systemic Anti-cancer Therapy Induced Diarrhoea in Adult Patients v2.3

Coversheet for Network Expert Advisory Group Agreed Documentation

This sheet is to accompany all documentation agreed by the West Midlands Strategic Cancer Alliance Expert Advisory Groups. This will assist the Clinical Network to endorse the documentation and request implementation.

EAG name	**Systemic Anti-cancer Therapy (SACT) Expert Advisory Group**	
Document Title	**Management of Systemic Anti-cancer Therapy (SACT) Induced Diarrhoea in Adult Patients**	
Published date		
Document Purpose	Assessment and management of Systemic anti-cancer treatment (SACT) induced Diarrhoea	
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References	Clatterbridge protocols - http://www.nwcscnsenate.nhs.uk/strategic-clinical-network/our-networks/cancer/cheshire-merseyside-clinical-network-groups/acute-o/ **UKONS Acute Oncology Initial Management Guidelines (2013). http://www.ukons.org/acute-oncology-forum (accessed 20.02.2017)** **UKONS Oncology/Haematology 24-Hour Triage Tool (V2 2016). http://www.ukons.org/reports (accessed 20.02.2017)** **CTCAE -** https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdfaccessed 25/4/17	
Consultation Process		
Review Date (must be within three years)	September 2020	
Approval Signatures:	**EAG Chair**  Date: 16.04.2018	**Network Clinical Director**  Date: 20.04.2018

Version History

Version	Date	Summary of Change/Process
0.1	October 2010	Document draft circulated for initial consultation to Chemotherapy Network Site Specific Group
0.2	October 2010	Reviewed by Dr Ian Geh Oncology Consultant at Queen Elizabeth Hospital
0.3	November 2011	Reviewed and updated by Frances Shaw
2.0	August 2016	Reviewed and updated Walsall Chemotherapy/ Acute Oncology team
2.1	April 2017	Reviewed by Nicky Adams (Acute Oncology Nurse Consultant) & Oncologists Dr Mikropoulos / Dr Kunene
2.2	September 2017	Further revision following comments from SACT Expert Advisory Group April 2017
2.3	April 2018	Further revision following comments from SACT Expert Advisory Group April 2017

Date for Review	**September 2020**

1. Scope of the Guideline

This guidance has been produced to support the following:

- Prevention and management of diarrhoea in adult patients receiving systemic anti-cancer treatment (SACT) including Immunotherapy
- The guidelines have been revised to incorporate the United Kingdom Oncology Nurses Society (UKONS) Initial management guidelines (Version 2.0 26/03/2018) (Appendix 1) And UKONS 24 hour oncology/haematology Triage (V2 2016)

2. Guideline Background

- Patients receiving Systemic Anti-cancer therapy (SACT) are at high risk of developing diarrhoea. This risk can be up to 80% with chemotherapeutic agents such as irinotecan and 5-fluorouracil (McQuade et al 2016). This is an unpleasant side effect which will affect the quality of life of a patient and is important that it is treated as effectively as possible.

- Diarrhoea may also lead to delays in treatment, dose reduction or discontinuation of therapy and the potential for admission to hospital. There is also a small but significant incidence of mortality with SACT induced diarrhoea. Hence it is essential that diarrhoea is treated effectively

- Watery diarrhoea is commonly associated with Cancer Immunotherapy (27-54%) and symptoms occur within a few days to weeks of therapy (Gupta et al, 2015). Diffuse acute and chronic colitis are the most common findings on endoscopy (8-22%). Concomitant infectious causes of diarrhoea must be evaluated. Most cases maybe successfully managed with discontinuation of Cancer immunotherapy and corticosteroid therapy. Those with persistent grade 2 and grade 3/4 diarrhoea should undergo endoscopic evaluation and require specialist gastroenterology opinion **(see appendix 3).**

- The combination of neutropenia and diarrhoea is potentially extremely serious and mortality risk is high for such a patient

Aims of patient care

- To minimise patient morbidity and reduce the risk of death associated with SACT induced diarrhoea
- To encourage patient compliance with treatment through minimising and controlling SACT induced diarrhoea
- To decrease the need for treatment related dose modification due to SACT induced diarrhoea

Objectives

- Encourage prompt diagnosis and initiation of treatment of SACT induced diarrhoea
- Maximise patient quality of life whilst on SACT throughout treatment minimising effects of diarrhoea
- Ensure patients receive an appropriate management strategy for their grade of diarrhoea. It is vital to read the Drug specific Information Sheet in addition to general diarrhoea guidance

3. Guideline Statements

Assessment of Diarrhoea

- Patients should be classified using the National Cancer Institute (NCI) CTCAE V4 outlined below
- Grading of diarrhoea will affect the overall assessment of toxicity for future dose delay or dose reduction
- Thorough systematic patient assessment is recommended using the revised version of the UKONS Oncology/Haematology 24-Hour Triage Tool (2016).Obtain history of onset and duration of diarrhoea including number of episodes in 24 hours, consistency, colour, associated symptoms, oral intake
- Consider medication profile including type of SACT, particularly immunotherapy, clearly identify if the patient has been taking laxatives or loperamide
- Consider dietary profile, to identify diarrhoea-enhancing foods
- Exclude alternative causes such as infection, bowel obstruction, malabsorption such as with pancreatic cancer, faecal impaction, acute radiation reaction

Table 1

Grades	1 (amber)	2 (amber)	3 (red)	4 (red)
Number of stools/day	**Up to 3 bowel movement a day over pre-treatment baseline**	**Up to 4-6 Episodes a day over baseline**	**Increase up to 7-9 episodes over baseline**	**Increase up to 10** Episodes a day
Stool	**Loose**	**Nocturnal stools**	**Incontinence Nocturnal/ bloody stools I**	**And / or grossly Bloody Stool/ or**
		In case of immunotherapy escalate gr 2 > treat as serious/ potentially life threatening see appendix 3		
If Stoma	**Mild increase in ostomy output**	**Moderate increase in stoma output (does not interfere with normal daily activity)**	**Severe increase in ostomy output (does interfere with normal daily activity)**	**Requires intensive support/ involvement (risk of haemodynamic collapse)**
Symptom		**Moderate cramping**	**Severe cramping**	**Need for Parenteral fluid support**

4. Risk Factors

Patient factors

- Older age
- Female gender
- Poor performance status > 2
- Associated bowel pathology such as lactose intolerance
- Presence of tumour in bowel

Therapy related factors

- Agent specific such as Irinotecan, Capecitabine
- Cancer Immunotherapy (eg auto-immune toxicity) (For example, Ipilimumab, Pembrolizumab, Nivolumab)
- Cancer growth inhibitors (TKI's) Erlotinib, Afatinib,
- Weekly chemotherapy schedule
- Infusional chemotherapy
- Prior history of cancer treatment induced diarrhoea
- Concomitant abdominal-pelvic radiation and chemotherapy.

5. Management (see appendices 1, 2 and 3)

- Interrupt / **STOP SACT, including Oral therapy until you have Discussed with the Acute Oncology Team or Oncologist.**
- Immediate fluid replacement/electrolytes plus / IV antibiotics if sepsis suspected as appropriate. Stop ACE inhibitors/diuretics/ NSAIDS / obtain stool sample

Medication

- Medication can be used to control the symptoms of SACT induced diarrhoea

Grade 1-2:

Loperamide

a) Loperamide SHOULD NOT be given to patients on immunotherapy without consultant advice

b) Loperamide should be used where grade 1 diarrhoea lasts more than 12 – 24 hours or for grade 2 diarrhoea; unless patients on cancer immunotherapy where this should be escalated to 'Red risk' as action for grade 3-4

c) Patients who develop diarrhoea on Irinotecan should immediately start on high dose loperamide unless within the first 24 hours of receiving treatment –see section 6.0

Standard Dose: 4mg initially followed by 2 mg after each loose stool to a maximum 16mg daily

d) If diarrhoea persists for more than 24 hours whilst taking standard dose loperamide patients should be commenced on codeine 30-60mg QDS see below.

e) Continue loperamide for 12 hours after resolution of diarrhoea but no more than 48 hours in total as risk of paralytic ileus with high dose/prolonged use.

Codeine
Codeine may be added or replace loperamide at the discretion of the physician for grade 1 – 2

Dose 30 – 60mg four times daily (maximum 240mg / 24 hours)

Grade 3-4 diarrhoea consider admission to hospital- follow management for Grade 3-4

Octreotide

a) Where grade 1 and 2 diarrhoea lasts more than 24 hours despite the use of high dose loperamide / codeine then octreotide should be considered.

b) Withhold if not on full maximal anti diarrhoeal medication prior to admission, but review every 12-24 hours.

c) Where a patient experiences grade 3 or 4 diarrhoea then octreotide is indicated and the patient should be hospitalized. The octreotide can usually be discontinued 24 hours after the end of the diarrhoea.

Standard Dose 100 – 150 microgram subcutaneously THREE times daily
Consult with Oncologist

Antibiotics

a) Intravenous antibiotics may be required where patients are neutropenic and have grade 3 to 4 diarrhoea (ciprofloxacin oral 500mg twice daily) and should be considered if grade 1 to 2 diarrhoea has not resolved after 24 hours.

Broad spectrum antibiotics should be considered (even if afebrile)

6.0 Management of diarrhoea due to irinotecan (see also appendix 2)

Atropine - Only Used in treatment of early diarrhoea with Irinotecan

- Early diarrhoea
  a) Early diarrhoea with irinotecan starts during or within 24 hours of receiving the dose. It is part of an acute cholinergic reaction and is usually accompanied by symptoms such as sweating, blurred visions, eyes and mouth start to water excessively and the patient feels dizzy and unwell. These symptoms can be controlled using a dose of 0.3mg subcutaneous atropine.
  b) These symptoms can be prevented with future courses of chemotherapy by the administration of the atropine prior to the dose of irinotecan. A further 0.3mg dose can be repeated if needed within the 24 hour period post irinotecan.
  c) Patients should not take their anti-diarrhoeal drugs (such as loperamide) within the first 24 hours but should contact their 24 hour advice line with a view to a medical review for the prescription of a second dose of atropine

- Delayed Diarrhoea
    a) Delayed diarrhoea occurs more than 24 hours after the dose of irinotecan. The patient should inform their place of treatment and start on appropriate treatment.
    b) The patient should drink plenty of fluids with electrolytes and the current recommendation is to start on high dose loperamide (4mg immediately then 2 mg every 2 hours to continue until 12 hours after the last loose stool).
    c) Loperamide must not be taken for more than 48 hours due to the risk of paralytic ileus.
    d) A prophylactic broad spectrum antibiotic such as Ciprofloxacin 250mg BD for 7 days should be considered where diarrhoea persists longer than 24 hours.

If severe diarrhoea persists longer than 48 hours or is associated with nausea, vomiting or fever patient should be admitted to hospital.

7.0 Patient Information and Counselling

Pre-treatment education

- All patients, and with their consent, their family members/friend should be given access to appropriate written information during their investigation and treatment, and on diagnosis will be given the opportunity to discuss their management with a clinical nurse specialist who is a member of the relevant MDT.
- Prior to starting treatment patients should be informed that diarrhoea is a potential side effect of cancer treatment , especially with certain drugs and if given in combination with other cancer treatment
- Patients receiving immunotherapy treatment should be advised to report early signs of diarrhoea as the management for immune-related diarrhoea is different (see appendix 3)
- Patients should be given advice when it is appropriate to contact the 24hr advice line regarding their diarrhoea.
- Patients may require nutritional advice and support in order to achieve a satisfactory nutritional status, dietician referral should be considered.
- Advice on dietary modification during diarrhoeal symptoms should be given: Refer to 'Dietary advice for adults having radiotherapy or chemotherapy' as described in the MacMillan leaflet: *www.macmillan.org.uk/information-and-support/coping/side-effects-and-symptoms/eating-problems/diarrhoea*

Patients should be advised to report any of the following

- Increase in frequency and volume (grade 2 or above as per CTC criteria) or relative increase from baseline
- Mucous in stools
- Fever associated with diarrhoea
- Abdominal cramps/pain/bloating (especially for patients receiving vinca-alkaloids)
- Dizziness
- Blood in stools
- Inability to drink adequate amounts of fluid

The patient must have a method of access for 24 hour advice at all times.

- Patients should be advised to document the frequency and consistency of their stools and monitor their temperature regularly.

- Patients taking oral SACT Medication must be informed that if they develop diarrhoea that does not settle with loperamide they MUST STOP TAKING ORAL SACT and call the urgent numbers given to them including contacting out of hours emergency contacts.

Patient Advice whilst having Diarrhoea:

Advise patient to:

- Drink copious amounts of liquid (up to two litres a day) to replace the fluid lost with the diarrhoea, but avoid alcohol, coffee, milk, and lactose products.
- Eat small, frequent meals made from low fibre foods a BRAT diet can be helpful (banana, rice, apples, toast).
- Eat meals slowly.
- Eat less fibre (cereals, raw fruits and vegetables) until the diarrhoea improves. Avoid fried or greasy food, raw vegetables, spicy foods like chilli peppers.
- Stop laxatives

Appendix 1

Guideline 6. DIARRHOEA (2 page guideline). Initial triage assessment within 15 minutes
A disorder characterised by frequent and watery bowel movements. Grading is relative to normal baseline function.

Identify: Patients who have received/receiving systemic anti-cancer treatment or are at risk of disease related immunosuppression or a history of stem cell transplant. These patients may be myelosuppressed / neutropenic and at risk of sepsis. If present, this should be managed as per guideline 12 on P.19-20
Observations: Calculate and monitor NEWS score.
Investigations: Urgent FBC, U&E + magnesium, LFTs, CRP, abdominal X-ray.
Stool sample for C&S/ova/cysts/parasites to rule out infective causes of diarrhoea-e.g. Campylobacter/salmonella and CDT screen.
Do NOT assume this is infective it is most likely to be drug induced in this group of patients
Questions:

- Is there a cancer diagnosis/primary disease?
- Is the patient taking anticancer treatment at the moment or recently? If so what treatment and when did it stop?
- Is the patient receiving radiotherapy to the abdomen or pelvis and when was their last treatment?
- How many stools a day above normal amount? or how much stoma output is there above normal amount? Have they had any nocturnal movements? For how many days have they had diarrhoea? Is it interfering with activities of daily living?
- Are stools/stoma outputs formed, loose or watery? Any faecal incontinence or urgency? Any blood or mucous in the stool?
- Is there any abdominal pain e.g., cramping pains coming in waves?
- Is the patient able to eat and drink normally? Are they passing plenty of clear urine?
- Does the patient have any other SACT related toxicities, e.g. mouth ulcers, mucositis, nausea/vomiting, red hands/feet?
- Has the patient taken any antibiotics recently or been in hospital recently?
- What medication have they taken? Have they taken any laxatives or anti-sickness medication **or** any anti-diarrhoeal medication in the last 24 hours? If so what?

Differential diagnosis includes:

- **Graft versus host disease** in stem transplant patients – contact transplant haematologist **urgently**
- **Secondary to SACT e.g.** 5FU or CAPECITABINE, IRINOTECAN, any TKI, please see next page and specific **DRUG INFORMATION SHEET** for further management guidance. **Consider DPD deficiency**
- **Gastrointestinal symptoms due to IMMUNOTHERAPY - proceed to guideline 21 on page 30 for further guidance**
- **Infection**
- **Constipation** with overflow
- **Radiotherapy –** secondary to treatment

Grade 1 Amber
Increase up to 3 bowel movements a day over pre-treatment baseline or mild increase in ostomy output

Grade 2 (Amber)
Increase up to 4-6 episodes a day over baseline or moderate increase in ostomy output or nocturnal movement or moderate cramping

Grade 3 (Red)
Increase up to 7-9 episodes a day or severe increase in ostomy output
* and/or incontinence * and/or severe cramping
* and/or bloody diarrhoea

Grade 4 (Red)
Increase > 10 episodes a day or grossly bloody diarrhoea

Review medication WITHHOLD DRUGS including any SACT that may be contributing until Acute Oncology or Site Specific team review
ESCALATE TO RED for any of the following:

- **Grade 2 and receiving or received immunotherapy treatment in the last 12 months**
- **Grade 2 for >24 hours despite anti-diarrhoeal medication**
- **Other symptoms e.g. temperature, nausea/vomiting, mouth ulcers, or clinical concerns**
- **Haematology patient**
- **Oncology -** Consider loperamide initially. If ineffective consider Codeine Phosphate. Reduce and then stop antidiarrheal after 12-24 hours free of diarrhoea.
- Review any other SACT toxicities according to guidelines.
- Review all medications and stop prokinetics and laxatives once constipation with overflow has been ruled out. Avoid domperidone and metoclopramide anti-emetics.

Patients with grade 3 or 4 diarrhoea require specialist secondary care to manage symptoms - IV resuscitation may be required. They should be admitted further assessment and active management.
WITHHOLD SACT until Acute Oncology Team review and review all other medication as they may be contributing – if receiving Capecitabine or 5FU consider DPD deficiency
If receiving or received immunotherapy treatment in the last 12 months - follow guideline 21 on page 30
Haematology patients – discuss with haematology team, urgently.
Further management detail on the page 13

Always make sure that the Acute Oncology Team are informed of the patients' assessment and/or admission as soon as possible. Immediate advice is available from the Acute Oncology Service or the 24 Hour Oncology on call rota.
WITHHOLD! SACT, including oral therapy until, you have discussed with the Acute Oncology or Site Specific Team.

Guideline 6 continued. **DIARRHOEA**

Initial Management

1. Consider infective diarrhoea:

Isolate until infection excluded

- Send stool sample urgently - Inform microbiology and discuss management with microbiologist
- If haematology patient or strong suspicion of infective diarrhoea, withhold anti-diarrhoeal medication until stool result available
- Give antibiotics according to local policy (e.g. for C.Difficile or neutropenic sepsis) **Consider** administering antibiotics empirically if not settling.

2. Consider graft versus host disease in stem transplant patients – contact transplant haematologist **urgently**

3. Secondary to SACT e.g. 5FU or CAPECITABINE, IRINOTECAN, ERLOTINIB any TKI or Targeted Therapy please see specific **DRUG INFORMATION SHEET** for specific management guidance.

4. Gastrointestinal symptoms due to IMMUNOTHERAPY - proceed to guideline 21 on page 30 for further guidance

5. Neutropenic Sepsis – if there is suspicion of, or potential for neutropenic sepsis start antibiotic management immediately as per policy (guideline 12 on pages 19-20) – do **not wait for FBC.**

6. IV fluid resuscitation. Replace fluid and electrolyte losses. Adjust on-going fluids according to fluid balance status and renal function.

7. Full medication review - Stop ACE-inhibitors/ diuretics/ NSAIDs. NB Folic Acid can potentiate and increase side effects of some SACT drugs

8. Nil by mouth (except sips) if abdominal pain or distension or abnormal abdominal X-ray

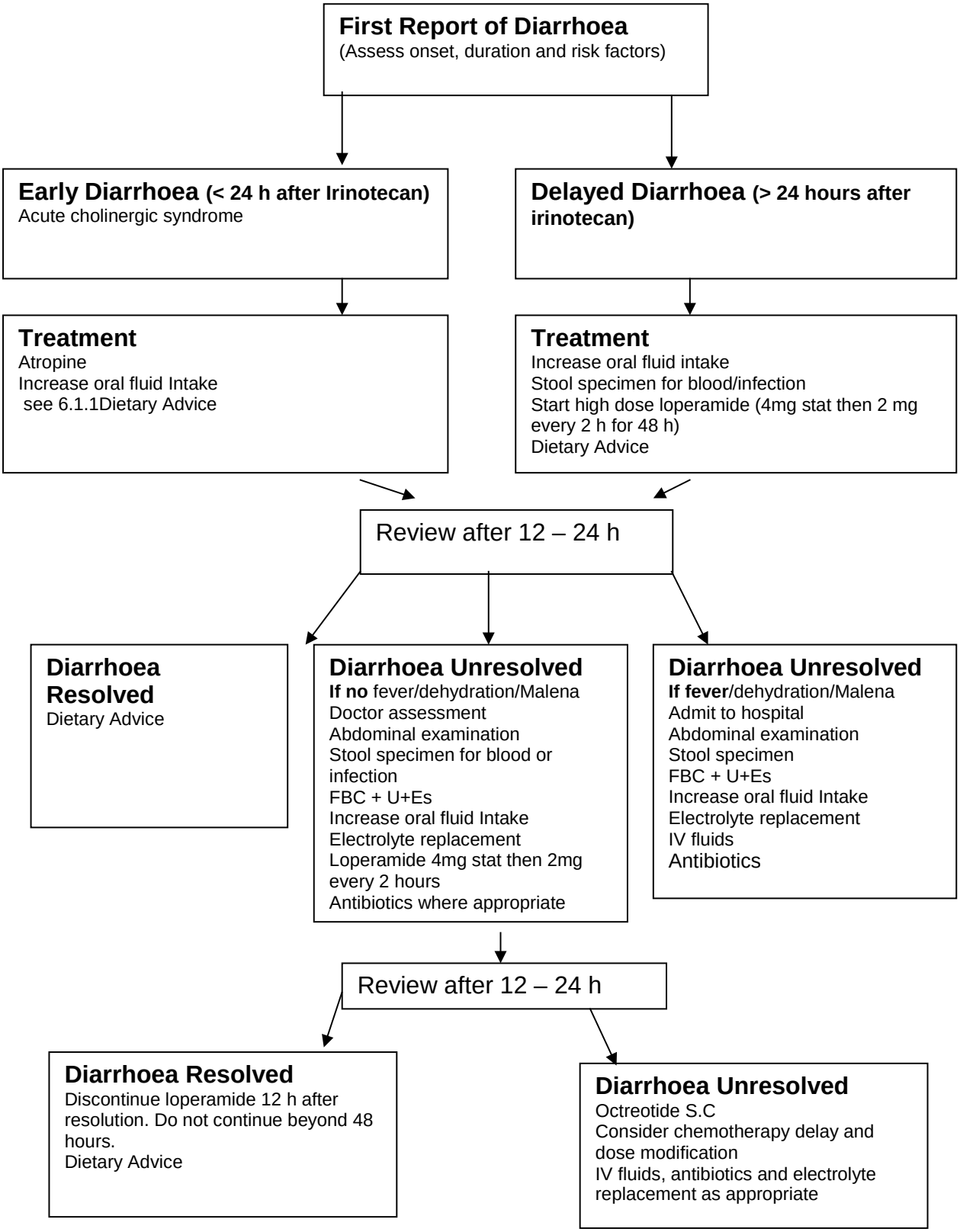
9. Antidiarrhoeal -

- **Haematology -** Discuss with haematology team on call before commencing antidiarrhoeal

- **Oncology:**
  - Consider loperamide 4mg initially then 2mg after each loose stool (maximum16mg per 24 hours) **N.B. Caution with high doses or prolonged use of loperamide as it can cause paralytic ileus**
  - If loperamide ineffective, then consider codeine phosphate instead of or in addition
  - Reduce/stop antidiarrhoeal after 12-24 hours free of diarrhoea.
  - If Grade 4 – consider the use of octreotide by sc injection and immediate IV broad-spectrum antibiotic (even if afebrile). Withhold if not on maximal antidiarrhoeal prior to admission but review every 24 hours.
  - Do not withhold antidiarrhoeal for more than 12-24 hours without thorough senior medical review.

10. Consider hyoscine butylbromide if abdominal spasms

Appendix 2 Diarrhoea – irinotecan



Appendix 3 **Diarrhoea –Immune- related Adverse Event**

Guideline 21. **Gastro Intestinal Immune-Related Adverse Event (irAE)**

Gastrointestinal (GI) irAEs are among the most common, 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.

As with all **irAEs** this can be a delayed effect of treatment and can occur up to 12 months after completion of treatment

Mild (Grade 1)

< 4 stools/day over baseline *or* mild increase in ostomy output

NO history of abdominal pain, mucous/blood in stools

Management Plan:

Investigations:

- Baseline bloods (FBC, U&E, LFTs, TFTs, cortisol & CRP)
- Stool microscopy and culture
- Clostridium difficile toxin
- Faecal calprotectin (if symptoms persist)

Treatment:

- Loperamide (use with caution as may mask symptoms of worsening colitis)
- Encourage fluids
- Avoid high fibre and lactose

Actions:

- Telephone assessment within 3 days
- Continue Immune checkpoint inhibitors unless on combination anti-PD1/CTLA4 then consider **withholding** treatment

Symptoms: PERSIST (≥5 days) or WORSEN or are associated with deranged U & E's

CAUTION – discontinue loperamide and/or codeine in patients with moderate to severe symptoms as these drugs increase the risk of colonic dilatation and perforation.

Moderate (Grade 2)

If **any** of the following symptoms are present:

- 4-6 stools/day over baseline *or* moderate increase in ostomy output
- Moderate abdominal pain/cramps/discomfort
- Mucous in stool regardless of number of stools
- Nocturnal stools
- Persistent grade 1 symptoms

Management Plan:

Investigations:

- Baseline bloods (FBC, U&E, LFTs, TFTs, cortisol & CRP)
- Stool microscopy and culture
- Clostridium difficile toxin
- Faecal calprotectin (if symptoms persist)
- Polymerase Chain Reaction **(PCR) screen**
- Abdominal X-Ray and consider CT abdomen/pelvis.

Treatment:

- Prednisolone 0.5-1 mg/kg/day + PPI cover
- STOP Loperamide and codeine
- Fluid balance and replacement as appropriate (inc. diarolyte sachets)

Actions:

- Withhold next dose of **ICPi**
- Daily telephone monitoring
- Gastroenterology advice/review

Assess response to treatment within 72 hours

Symptoms: Resolve or Improve to Mild See steroid tapering guidance

PERSIST
WORSEN
RELAPSE

Severe or Life-Threatening (Grade 3 + 4)

If **any** of the following symptoms are present:

- ≥6 stools/day over baseline *or* significant increase in ostomy output
- Severe abdominal pain
- Fever
- Dehydration
- Blood in stool
- Incontinence
- Limiting ADLs
- Episodes within 1 hour of eating

Admit patient

Investigations:

- Baseline bloods (FBC, U&E, LFTs, TFTs, cortisol & CRP)
- Stool microscopy and culture
- Clostridium difficile toxin
- Faecal calprotectin (if symptoms persist)
- Daily bloods (FBC, U&E, LFTs & CRP)
- CT Abdomen/pelvis
- Flexible sigmoidoscopy with biopsies (inc. CMV staining)
- Screen for Infliximab administration suitability on admission to avoid delay if treatment is required (to include-TB Eli spot test, hepatitis screen, HIV, chest X-Ray (if chest CT not already performed)

Refer and review by gastroenterologist

Treatment:

- IV hydration and fluid balance
- IV Methylprednisolone 1-2 mg/kg/day + PPI cover
- Antibiotics are not required as standard
- STOP loperamide and codeine

Use analgesia with CAUTION

Actions:

- Daily stool chart
- Consider nothing by mouth or clear fluids
- Dietician review
- Withhold and consider discontinuation of **ICPi**

PERSIST ≥ 3 days IV corticosteroids

Review patient daily, if no improvement within 72 hours, seek further urgent gastroenterology advice/opinion for management with infliximab.

Inform the Acute Oncology Team of the patients' assessment and/or admission as soon as possible.
Immediate advice is available from the Acute Oncology Service or the 24 Hour Oncology on call rota.
WITHHOLD! SACT, including oral therapy until, you have discussed with the Acute Oncology or Site Specific Team.

References

Gupta A, De Felice KM, Loftus EV, and Khanna (2015), Systematic Review: colitis associated with anti-CTLA-4 therapy, *Alimentary Pharmacology and Therapeutics,* 42 (4)

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