CHEMOTHERAPY TOXICITY AND COMPLICATIONS - DIARRHOEA

1 INTRODUCTION

Diarrhoea can be a debilitating, and potentially serious, consequence of chemotherapy or abdominal radiotherapy. Urgent investigation of the underlying cause, to exclude infection and ascertain the extent of damage to the GI tract, is essential.

Diarrhoea, even without fever, can be a symptom of severe infection in the neutropaenic patient. See **'**Guidelines for the Management and Prevention of Infection in Oncology and Haematology Patients.'

2 POTENTIAL CAUSES

These are divided into non-infective and infective causes.

2.1 Non-Infective

Cause	Features
Mucositis secondary to chemotherapy	Low volume, often with nausea and anorexia. Severity depends on type of chemotherapy. High dose methotrexate, cytarabine and anthracyclines are particularly high risk agents.
Medication	E.g. cisplatin, cytarabine, fludarabine, methotrexate, some antibiotics, laxatives, metoclopramide, irinotecan.
Constipation with overflow	Extensive faecal loading may be seen on plain abdominal X ray (not recommended routinely).
Radiation enteritis	May occur during abdominal or pelvic radiotherapy. Can also occur as a late complication following radiotherapy.
Non-infective causes not related to oncological diagnosis	E.g. appendicitis.

2.2 Infective

Cause	Features
Viruses	Rotavirus, Enteric Adenovirus, Astrovirus, Norovirus, Sapovirus. Stem cell transplant patients (particularly allografts) are, in addition, particularly at risk from HSV and CMV (may cause bloody diarrhoea). In such cases discuss with Microbiology/Infectious Disease Consultant and consider PCR based test as well as other investigations e.g. bowel biopsy in severe or protracted cases.
Parasites	*Cryptosporidium spp.*, *Giardia lamblia*, *Entamoeba histolytica* can all cause diarrhoea, but not commonly. *Cryptosporidium* can be life-threatening in the immunocompromised patient.
Bacteria	*Salmonella, Shigella, Campylobacter, E.coli 0157* Also: bacterial causes responsible for diarrhoea may be a symptom of onset of septic shock- see introduction above.
Clostridium difficile	Toxin related symptoms– rare in young children.
Clostridium septicum	Associated with neutropaenic enterocolitis (diagnosed from blood culture not stool).

3 INVESTIGATION

1. Thorough assessment including history and clinical examination.

2. Check electrolytes and glucose (BM on the ward in an ill child in addition to oncology profile). Beware of possible hypoglycaemia.

3. Document volume, consistency, colour and presence of mucous or blood in stool. Use **Bristol Stool Chart.** https://www.nice.org.uk/guidance/cg99/resources/bristol-stool-chart-pdf-245459773

4. In general, in reasonably well patients with diarrhoea, stool samples are NOT required to be sent for virology or bacteriology. A previous service evaluation[1] on the Oncology Unit showed no utility in routinely sending stools for MC + S (bacteriology). A similar service evaluation[2] showed no benefit for routinely testing stools for rotavirus, since the introduction of routine rotavirus vaccination in the UK.

5. Testing for infectious causes of diarrhoea should be considered and approved by an Oncology/Haematology Consultant or Registrar and where appropriate a Consultant Microbiologist/Infectious Disease Consultant.

6. Testing is particularly indicated in:

    a) Patients with severe or prolonged diarrhoea e.g. not improving after 3-5 days
    b) Patients with abdominal symptoms or signs e.g. pain, distension
    c) High risk patient groups e.g. Stem Cell Transplant patients
    d) Patients with blood-stained or mucousy stools

7. In such cases, a stool sample should be sent using the Meditech order:–
   a) **Faeces-Culture** (basic [non-concentrated] microscopy and cryptosporidium smear; bacterial culture). The Microbiology Laboratory will send away samples from oncology/haematology patients for viral PCR (rota, adeno, noro, astro and sapovirus) to a designated laboratory if appropriate.
   b) Consider discussion with Microbiology/Infectious Disease Consultant

8. New onset diarrhoea occurring in an in-patient after 72 hours will be considered possible hospital acquired diarrhoea. In such cases test for *Clostridium difficile* (see **'**Guidelines for the Management and Prevention of Infection in Oncology and Haematology Patients') and FCV. Note: standard bacterial culture will not be done as per standard Trust policy for hospital acquired diarrhoea.

9. In children over 2 years of age, and particularly in teenagers, *Clostridium difficile* associated diarrhoea (CDAD) should always be considered. A falling albumin, raised lactate or abdominal distention can be signs of CDAD. If there is a strong clinical suspicion of *C. difficile* infection, but the *C. difficile* toxin test is negative, a single repeat sample should be sent for re-testing after 24 hours.

10. Norovirus should be considered if there are also staff members who are ill with diarrhoea and vomiting. Use the in-house norovirus PCR test that can be requested following discussion with IPC team.

11. Urgent Abdominal USS +/-abdominal x-ray and surgical review if abdominal pain and/or tenderness in neutropaenic patient and typhlitis suspected. In some cases CT should be considered.

12. A plain abdominal X-ray if constipation with overflow or a surgical pathology like bowel obstruction is suspected.

13. If symptoms recur or persist for 7 days in the absence of a positive culture, consult gastro-enterology team with a view to additional investigations including upper and lower GI endoscopy.

4 MANAGEMENT

4.1 General Principles

1. Isolation and hand hygiene (by patient, carers and staff) until the aetiology is known are important measures to prevent the spread of infection. All patients with diarrhoea should be isolated and placed under contact precautions until their symptoms have resolved for at least 48 hours.

2. Enteral feeding will exacerbate diarrhoea related to mucositis because of fat and carbohydrate malabsorption. However, as luminal nutrients are needed for gut repair it is desirable to continue enteral feeds if possible.

3. Keep patient NBM if typhlitis suspected at least until surgical review and Oncology/ Haematology Consultant review.

4. Use local protective measures to prevent skin breakdown, secondary infections and discomfort.

4.2 Treatment

4.2.1 If there are signs of shock due to >10% dehydration

1. Inform the ST4+ doctor or consultant immediately.

2. Oxygen should be administered to maintain adequate oxygen saturation, if necessary.

3. Give an IV fluid bolus - 20 ml/Kg of 0.9% sodium chloride and reassess.

4. Discuss with Consultant. Consider second IV fluid bolus - 20 ml/Kg of 0.9% sodium chloride.

5. If second fluid bolus required - inform ICU.

6. Review of patient by a haematology/oncology registrar grade or above and discuss subsequent management with ICU staff as appropriate.

7. Monitor vital signs and urine output closely (half hourly to hourly depending on patient status). Urinary catheterisation may be necessary if no urine output, despite improvement in haemodynamic status.

4.2.2 Neutropaenia associated diarrhoea in a febrile patient

Commence treatment with antibiotics in accordance with '**Guidelines for the Management and Prevention of Infection in Oncology and Haematology Patients'.**

4.2.3 Fluid Balance in unwell patients with severe diarrhoea

1. Pay attention to fluid balance, acid base balance and electrolyte levels.

2. Replace fluids with maintenance fluid using Plasmalyte 148 with 5% glucose and replace estimated fluid deficit with 0.9% sodium chloride.

3. Be aware of fluid pooling in the gut if total fluid input > output and low BP.

4. Plasmalyte 148 with 5% glucose contains potassium 5mmol/L. If potassium replacement is required refer to Clinical Guideline on the Administration of Intravenous Fluids or Medicines Management Code Section 49.2 – Treatment of Hypokalaemia in Paediatric Oncology Patients on the Oncology/Haematology Unit.

5. Monitor electrolytes at least 12 hourly in severe cases.

4.2.4 Feeds

1. Consider whether feeds need to be reduced or stopped.

2. Discuss the most appropriate feeds with a dietician.

3. TPN should be started for severe mucositis with an anticipated duration of more than 7 days, or in the malnourished child. Try enteral feeds via nasogastric tube (or PEG if in situ) prior to starting TPN.

4.2.5 Other Drug Therapy

Stop any exacerbating drugs if possible.

4.2.6 Diarrhoea Post Irinotecan

If diarrhoea develops within 8 hours of receiving irinotecan administer IV atropine and inform the relevant consultant. For late onset diarrhoea (after 24 hours) use loperamide as prescribed.

4.2.7 Loperamide

Treat with loperamide only if cultures are negative and there is no blood in the stools.

Loperamide		
Age: 1 month-1 year Cautious use in under 3 year Olds	1-12 years Cautious use in under 3 year olds	12-18 years
100-200 microgram/kg twice daily Increased if necessary up to 2mg/kg/day	100-200 microgram/kg 3-4 times a day, Increased if necessary up to 1.25mg/kg/day (Max 16mg/day)	2-4mg 2-4 times a day (Max 16mg/day)

If the diarrhoea is still not controlled on maximum loperamide dose discuss with consultant regarding further management. Note that loperamide liquid contains glycerol as an excipient. Large quantities of glycerol may cause diarrhoea as a side effect.

4.2.8 *Clostridium difficile* suspected or detected

Refer to **'Guidelines for the Management and Prevention of Infection in Oncology and Haematology Patients'.**

4.2.9 Virus Detected

Specific treatment should be considered in patients with adenovirus, CMV, HSV (and possibly rotavirus). This should be the decision of the consultant. Refer to '**Guidelines for the Management and Prevention of Infection in Oncology and Haematology Patients'.**

4.2.10 Chronic Diarrhoea

The gastroenterology team should be consulted for patients with intractable / chronic diarrhoea with a view to endoscopy and gut biopsies.

References

1. O'Connor O, Cooke RP, Cunliffe NA, Pizer B. Clinical value of stool culture in paediatric oncology patients: hospital evaluation and UK survey of practice. *J Hosp Infect.* 2016 Jan;95(1):123-125.

2. Akhtar T, Cargill J, Gerrard C, Shaw F, Cunliffe NA, Cooke RPD, Pizer B. Detection of rotavirus in paediatric oncology patients with diarrhoea: the impact of rotavirus vaccine. *J Hosp Infect.* 2018; 99(2) 185-187.

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Section Number	Page Number	Revision(s) made	Reason for revision(s)
3	2	Point 3 Link to Bristol Stool chart added	For clarification
3	2	Point 4 References for service evaluations added	For clarification
3	3	Point 7a Meditech order updated to Faeces-Culture Laboratory samples sent away to removed	Change to in-house testing for viral enteric pathogens. Laboratory samples sent away to likely to change again in the near future