Atlantic Provinces Pediatric Hematology/Oncology Network
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Reviewed and approved by specialists at the IWK Health Centre, NS, and the Janeway Children's Health and Rehabilitation Centre, NL

Guidelines on the Prevention and Management of Chemotherapy Associated Diarrhea

APPHON/ROHPPA supportive care guidelines have been developed by appropriate Atlantic Provinces health professional specialists (physicians, pharmacists, nurses and other health professionals) using evidence-based or best practice references. Format and content of the guidelines will change as they are reviewed and revised on a periodic basis. Care has been taken to ensure accuracy of the information. However, any physician or health professional using these guidelines will be responsible for verifying doses and administering medications and care according to their own institutional formularies and policies and acceptable standards of care.

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OVERVIEW:

Diarrhea is one the main morbidities for children treated for cancer. If not properly treated diarrhea can be life threatening, especially if the patient is neutropenic. Possible etiologies include both secretory diarrhea (chemotherapy, radiotherapy, decreased physical activity, graft versus host disease (GVHD), infections) and osmotic diarrhea (e.g. associated with lactose intolerance). The mechanism of diarrhea caused by chemotherapy and abdominal/pelvic radiation occurs as a result of mucosal damage which results in decreased absorption of water and electrolytes, causing diarrhea. After excluding the causes above, bile salt malabsorption also needs to be considered (associated with cramping and watery diarrhea due to colonic irritation by excess bile salts).

The scope of this consensus document is the pathophysiology, risk factors and management of chemotherapy-induced diarrhea (CID) in children.

CHEMOTHERAPY INDUCED DIARRHEA:

CID can be debilitating and, in some cases, life threatening. Findings in such patients include volume depletion, renal failure, and electrolyte disorders such as metabolic acidosis and depending upon water intake, hyponatremia (increased water intake that cannot be excreted because of the hypovolemic stimulus to the release of antidiuretic hormone) or hypernatremia (insufficient water intake to replace losses).

CID is defined as an increase of at least 2 to 3 or more (loose) stools per day or causing waking at night or an increase in loose, watery stool output compared with before treatment.

Chemotherapy induced diarrhea is caused by a combination of mechanical and biochemical disturbances stimulated by chemotherapeutic effects on the bowel mucosa. It can occur after any chemotherapy but is more common after the administration of Irinotecan (as high as 45%) and with high dose methotrexate.

Careful assessment should assist early recognition of chemotherapy induced diarrhea. Early treatment may prevent hospital admission.

Health promotion during the patient's first chemotherapy visit with advice on maintaining and maximizing health during treatment through adequate fluid intake, healthy diet, and prompt reporting of side-effects, may also reduce the incidence and severity of diarrhea.

GRAFT VERSUS HOST DISEASE (GVHD) INDUCED DIARRHEA:

Patients who undergo an allogeneic stem cell transplant are at risk for graft versus host disease, which is the host's response to the donor T-cells and often results in inflammation of the gut. Acute GVHD can present with engraftment following the transplant. GVHD may involve the whole gastrointestinal tract and can result in diarrhea, intestinal bleeding, cramping abdominal pain, and ileus. The diarrhea is typically green, mucoid, watery, and mixed with exfoliated cells forming fecal casts. Voluminous secretory diarrhea may persist despite cessation of oral intake. Beyond 100 days post BMT, GVHD is considered chronic although it may manifest with more acute symptoms. In the absence of features fulfilling criteria for the diagnosis of chronic GVHD, the persistence, recurrence, or new onset of characteristic skin, gastrointestinal tract or liver abnormalities should be classified as acute GVHD regardless of the time after transplantation.

Chronic GVHD (cGVHD) of the gut may manifest with diarrhea. Common features for cGVHD include malabsorption, anorexia, failure to thrive, and oral manifestations. It is typically though not always diagnosed beyond 100 days. Also note that it is not uncommon to have GVHD (either acute or chronic) present with co-infection. This should be considered in all patients.

The work up and management of diarrhea in allogeneic BMT patients is specialized and should always be done in conjunction with the pediatric BMT physicians.

RISK FACTORS FOR CHEMOTHERAPY INDUCED DIARRHEA:

- Female gender
- Associated bowel pathology (e.g. colitis, lactose intolerance)
- Concomitant abdominal-pelvic radiation
- Prior history of CID
- Prior history of neutropenic typhilitis

DIFFERENTIAL DIAGNOSIS:

Before addressing chemotherapy-induced diarrhea exclude diarrhea associated with the following:

- Infective episodes including Clostridium difficile and Candida
- Subacute obstruction
- Partial bowel obstruction
- Malabsorption
- Fecal impaction
- Constipation with overflow
- High osmolality diets (e.g. amino acid-based), lactose intolerance.
- Medications (e.g. stool softeners, laxatives, antibiotics, antacids etc)

CHEMOTHERAPY INDUCED DIARRHEA CAUSED BY IRINOTECAN:

Irinotecan is converted to its active metabolite SN38 in the intestinal lumen, which is subsequently glucuronidated in the liver to SN38G. SN38 induces direct mucosal damage in the intestine. The luminal environment altered by Irinotecan may favor different genera of bacteria allowing them to proliferate. Based on the assumption that bacterial beta-glucuronidase in the intestine is essential for activating SN-38G, antibiotics such as 3rd generation cephalosporins prevent E.coli bacteria from glucuronidation of SN-38G and thus reduce the activity of the toxic metabolite of irinotecan.

MANAGEMENT OF CHEMOTHERAPY-INDUCED DIARRHEA (Refer to flow diagram in Appendix 1)

1. All patients presenting with diarrhea should have their weight and hydration status documented and CBC, BUN, serum creatinine, sodium, potassium, chloride, calcium, magnesium and venous blood gas checked.

2. Microbiology investigations:
   A) Outpatients presenting with diarrhea should have consideration for:

i. Stool submitted for enteric virus testing
   - Rotavirus + Adenovirus EIA screening + Norovirus molecular detection (if Rota/Adenovirus negative)
ii. Stool culture or molecular assay for enteric bacterial pathogens
iii. Verotoxin (or Verotoxin gene) if bloody diarrhea or epidemiological / clinical suspicion/risk factors.
iv. Stool for ova and parasite examination (uncommon cause).

B) Inpatients developing diarrhea after being in hospital for greater than 72 hrs are extremely unlikely to have an enteric bacterial pathogen and stool testing should start with:

i. Stool submitted for enteric virus testing
   - Rotavirus + Adenovirus EIA screening + Norovirus molecular detection (If Rota/Adenovirus negative)

C) All patients (inpatients or outpatients) who develop diarrhea during or immediately after antibiotic therapy should have stool testing for *Clostridium difficile* toxins or toxin genes.

D) Stool Electron Microscopy or extended enteric virus molecular detection panels are typically reserved for highly immunosuppressed patients with prolonged diarrhea when the above investigations are negative. Discuss with Microbiologist.

E) Routine Diagnostic imaging is not usually required. Consider the following based on history and clinical exam: abdominal X-ray, upper gastrointestinal and small bowel follow through (rarely, as the osmotic effect of enteral contrast may worsen diarrhea), and/or abdominal ultrasound. Surgery or gastroenterology consultation as necessary.

3. Fluid replacement should be encouraged with an oral intake of at least maintenance volume of fluid appropriate for weight/age:
   For infants, breast milk or infant formulas are indicated but if not tolerated then Oral Rehydration solution (ORS) should strongly be considered.
   For older children, ORS is preferred over water-only. Soft drinks, high-energy or sports drinks may not provide appropriate electrolyte and glucose mixtures for the diarrheal losses incurred.

4. If unable to tolerate oral fluids or the patient has moderate to severe dehydration, admit for parenteral rehydration.

5. If neutropenic, consider broad spectrum antibiotic coverage with or without metronidazole in consultation with pediatric oncology.

6. If febrile and neutropenic, commence febrile neutropenia guideline in consultation with pediatric oncology.

7. If diarrhea is persistent and repeated wider spectrum stool cultures are negative AND patient is afebrile AND not neutropenic cautiously consider antidiarrheal agents.

GRADING DIARRHEA ACCORDING TO CTCAE V4.03:

Grading of diarrhea for children with chemotherapy induced diarrhea should follow the criteria established by the National Cancer Institute in the Common terminology criteria for adverse events (Appendix 2). Each Children's Oncology Group treatment protocol has dose modifications listed, either by drug or by toxicity. The Pediatric Oncologist is responsible for recommending dose modification of chemotherapy based on the below criteria and per the protocol specific criteria.

NOTE: *Do not prescribe antidiarrheal agents if gastroenteritis is suspected. Dietary modifications should be followed in conjunction with antidiarrheal agents (Appendix 3). Consider stopping any non-chemotherapy agents that can cause diarrhea (Appendix 4)*

ANTI-DIARRHEA AGENTS:

Although many other anti-diarrheals are available, the agents discussed below have shown some evidence in the treatment of chemotherapy-induced diarrhea in children.

1. Opioids:

a. **Loperamide**: a synthetic opiate derivative, is the initial drug of choice for CID. Loperamide acts as an antidiarrheal agent by exerting agonistic effects on opioid receptors in the GI tract, resulting in decreased peristalsis and increased fluid reabsorption. Loperamide is minimally absorbed and produces a limited side-effect profile. Although rare, loperamide can cause a paralytic ileus, and patients should be routinely monitored for this while using high-dose loperamide. Other side effects include abdominal pain, dry mouth, drowsiness, and dizziness. Although loperamide has been proven to be extremely effective in uncomplicated diarrhea, its utility as monotherapy for severe diarrhea is limited.

   The recommendation in current treatment guidelines is based on an effective reduction in fecal incontinence, frequency of bowel movements and stool weight.

   - Loperamide is indicated for Grade 1 diarrhea that persists for more than 12-24 hours or for moderate diarrhea (Grade 2).
   - Loperamide should be continued for 12 hours following resolution of the diarrhea and re-establishment of a normal diet.
   - High-dose loperamide is also recommended at the onset of any diarrhea in patients receiving Irinotecan chemotherapy.
     Note: Follow chemotherapy orders for when to start loperamide and what dose to give for Irinotecan induced diarrhea.

b. **Diphenoxylate- Atropine:** In consultation with pediatric oncology: 0.3-0.4 mg/kg, every 6-8 hrs added to loperamide therapy for Grade 1 or 2 diarrhea. This agent is **NOT** sufficient for the management of Grade 3 or 4 diarrhea.

2. Anti-Secretory Agents:

a. **Octreotide:** Is a synthetic somatostatin analog, that acts via several mechanisms including; decreased secretion of a number of hormones, such as vasoactive intestinal peptide; prolongation of intestinal transit time and reduced secretion and increased absorption of fluid and electrolytes. Octreotide is beneficial in patients with CID from

irinotecan. Octreotide is generally reserved as second-line treatment for patient's refractory to loperamide escalation due to cost.

Note: Follow chemotherapy orders for when to start octreotide and what dose to give for Irinotecan induced diarrhea and call the Pediatric Oncologist.

3. Anticholinergics:

a. **Atropine:** Is used in the treatment of early diarrhea (i.e. those with the presence of an acute cholinergic reaction with Irinotecan).

Note: Follow chemotherapy orders for when to start atropine and what dose to give for Irinotecan induced diarrhea and call the Pediatric Oncologist.

4. Other:

a. **Antibiotics:** Widespread inflammation and necrosis in the bowel predisposes patients to infections from opportunistic pathogens, especially if they are immunocompromised or neutropenic. Increased epithelial permeability, as well as a reduced immune system, enable microflora to translocate out of the gastrointestinal tract, predisposing patients to potential life-threatening gram-negative sepsis. Broad spectrum antibiotics should be considered in children who are unwell and neutropenic with diarrhea in consultation with a pediatric oncologist.

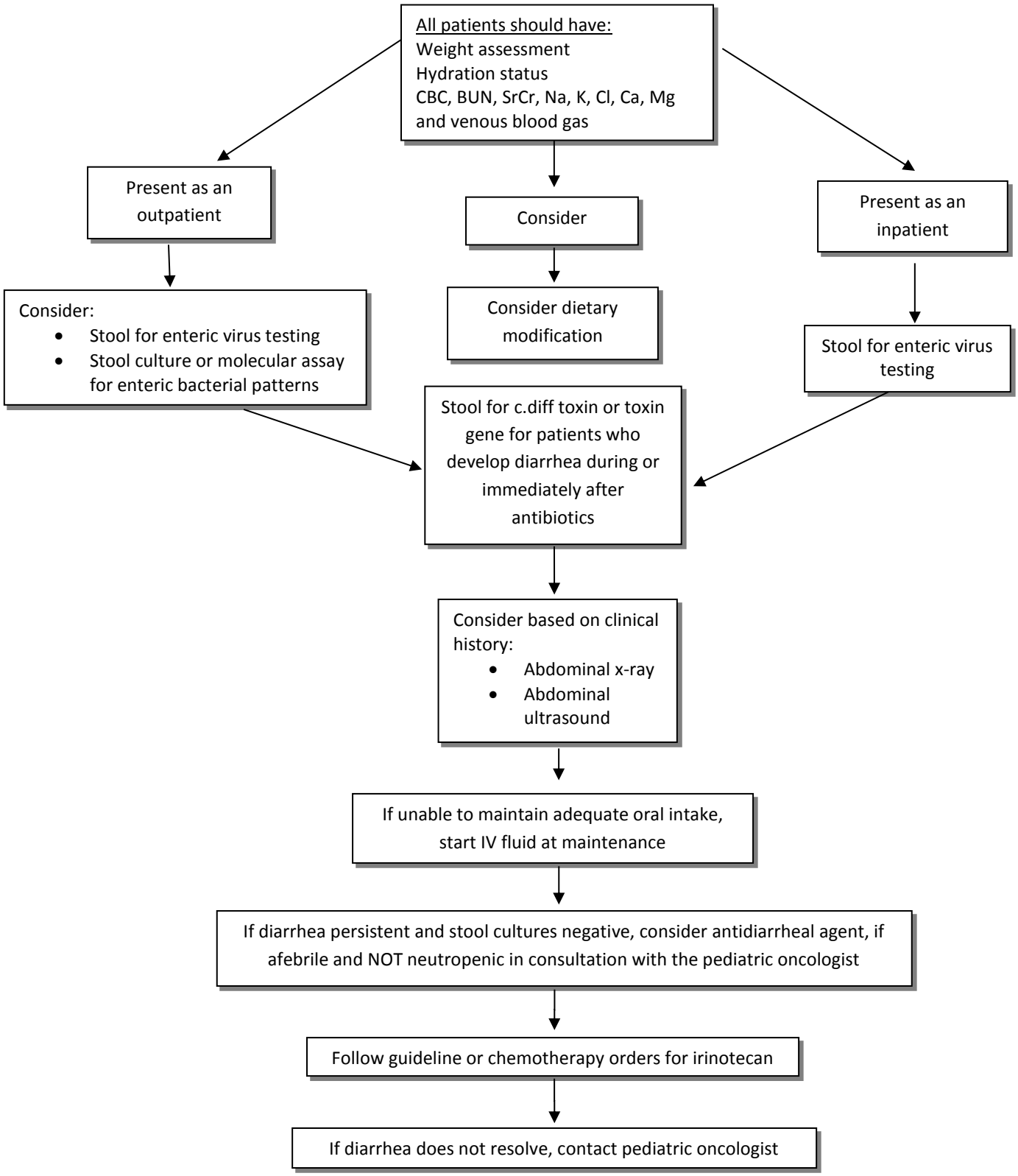
b. **Probiotics:** nonpathogenic microorganisms such as Lactobacillus rhamnosus, Lactobacillus acidophilus, and Bifidobacterium, have been extensively studied in the prevention of diarrhea. The possible mechanisms of action include providing a protective physical barrier from infectious bacteria, degrading carcinogens, and producing anti-inflammatory effects on the bowel mucosa. Immunocompromised patients should, however, be cautious of severe infections, such as sepsis, resulting from the use of probiotics.

Note: Given there is evidence to suggest probiotics may be beneficial in antibiotic induced diarrhea, probiotics should only be prescribed in consultation with pediatric oncology and gastroenterology.

c. **Sucralfate**: For diarrhea associated with pelvic radiation sucralfate should be considered.

APPENDIX 1

Management of Chemotherapy Induced Diarrhea in Children with Cancer



APPENDIX 2

National Cancer Institute Common Terminology Criteria for Adverse Events

Table 1: NCI CTCAE v4.03 Diarrhea

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhea	• Increase of less than four stools per day over baseline; • mild increase in ostomy output compared with baseline	• Increase of four to six stools per day over baseline; • moderate increase in ostomy output compared with baseline	• Increase of seven or more stools per day over baseline; • incontinence; • hospitalization indicated; • severe increase in ostomy output compared with baseline; • limiting self-care activities of daily living	• Life-threatening consequences; • urgent intervention indicated	Death

Diarrhea is characterized by frequent and watery bowel movements.
NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events.
Reproduced from: Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, June 2010, National Institutes of Health, National Cancer Institute. Available at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf (Accessed October 22, 2013).

APPENDIX 3

Dietary Modifications During Diarrhea

- Increase intake of clear fluids (e.g. water, sports drinks, broth, clear juices (excluding apple juice), and decaffeinated tea.
- Recommend oral rehydration solutions as indicated.
- Limit milk and lactose products temporarily to see if this improves symptoms
- Avoid spicy, fried, greasy, fatty foods, raw vegetables, caffeine (tea, coffee, alcohol) and carbonated drinks.
- Advise increasing soluble fiber in the diet including; oats, barley, rice, carrots, banana, applesauce, papaya, sweet potato/yams, turnip, beets, mushrooms, squash and turnip and decreasing insoluble fiber such as bran, whole grain cereals/breads/pastas, prunes, pears, berries and remove the skin and seeds from all fruit/vegetables
- A BRAT (banana, rice, apples, toast) diet can be helpful.
- Referral to a dietician should be considered.
- In refractory and hard to treat cases consult pediatric gastroenterology. Consider underlying immunodeficiency syndrome.

APPENDIX 4

Non-Chemotherapy Drugs that can Cause Diarrhea that are commonly prescribed for pediatric cancer patients include but are not limited to:

1. Antacids with magnesium
2. Antibiotics, e.g., ampicillin, erythromycin, amoxicillin, ciprofloxacin, levofloxacin
3. Bile salts, lactulose
4. Potassium chloride
5. Prokinetic agents
6. H-2 blockers, proton pump inhibitors

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External reviewers (anonymous):

An anonymous external review of this guideline was conducted throughout Atlantic Canada by APPHON/ROHPPA. Twenty-two health care professionals responded to the external review, including hematologists/oncologists, nurse manager ED, nurse Practitioner, registered nurses, pediatricians, pharmacists and 4 other undisclosed health care professionals. One review came from a group of multi-disciplinary health care workers.

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