APPHON/ROPPHA Guideline for the Prevention and Management of Chemotherapy Induced Nausea and Vomiting in Children with Cancer

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PEDIATRIC HEMATOLOGY/ONCOLOGY SERVICE

The 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. This guideline is to provide health care providers with an approach to the prevention and management of chemotherapy induced nausea and vomiting in children with cancer. 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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The recommendations in this guideline are adapted to the local context from the C17 endorsed Pediatric Oncology Group of Ontario (POGO) Guideline for the Prevention of Acute Nausea and Vomiting due to Antineoplastic Medication in Pediatric Cancer Patients, the POGO Guideline for Classification of the Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Cancer Patients, and the POGO Guideline for the Prevention and Treatment of Anticipatory Nausea and Vomiting due to Chemotherapy in Pediatric Cancer Patients. The full versions of the guidelines which include the systematic reviews are available at: **http://www.pogo.ca/healthcare/practiceguidelines/**

The APPHON/ROHPPA guideline utilized these systematic reviews and adapted the information for use in the Atlantic Provinces. The APPHON/ROHPPA guideline provides recommendations on the management of nausea and vomiting in children being treated for cancer or chemotherapy induced nausea and vomiting (CINV). The guideline will include the management of acute, delayed, anticipatory, breakthrough and refractory CINV. This guideline will also categorize antiemetic therapy based on the emetogenic potential of chemotherapy agents. The Pediatric Oncology Group of Ontario (POGO) has classified chemotherapy agents based on their emetogenic potential. This guideline will not include a review of alternative methods of nausea control nor will it make recommendations as it is felt the evidence in this area is not sufficient.

The target audience of this guideline is the healthcare providers involved in the care of children with cancer in the Atlantic Provinces. This document is a general reference and is not intended to replace good clinical judgment.

Guideline for the Prevention and Management of Chemotherapy Induced Nausea and Vomiting in Children with Cancer

Definitions:

Types of nausea and vomiting (which includes retching) will be discussed in this guideline:

- Acute: most commonly begins within 1-2 hours of chemotherapy and peeks around 4-6 hours and resolves within 24 hours
- Delayed: occurs more than 24 hours and usually within 7 days after chemotherapy.
- Anticipatory: Occurs before the patient receives chemotherapy and is thought to be associated with previously poorly controlled nausea and vomiting.
- Breakthrough: Occurs when prophylactic antiemetics are not effective and the patient requires use of additional rescue medications.
- Refractory: Occurs when antiemetics no longer work to control nausea and vomiting. This usually happens after a few or even several chemotherapy treatments.

The four categories of emetogenic potential:

1. High: CINV in greater than 90% of patients.
2. Moderate: CINV in 30-90% of patients.
3. Low: CINV in 10-30% of patients.
4. Minimal: CINV in less than 10% of patients.

Nausea and vomiting assessment:

The heath care provider or parent must document vomiting daily and record frequency and volume if possible.

Nausea can be assessed using the PeNAT tool (Figure 1 & Figure 2). This is a validated tool of faces in children 4 years and older. It is a scale of 1-4 where 1 is no nausea and 4 is severe nausea. The tool also incorporates a few questions (Figure 2) to determine the language that each family uses to describe nausea and vomiting.

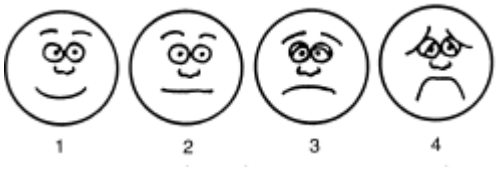


Figure 1 – Faces used for administration of the Pediatric Nausea Assessment Tool to children older than 8 years. Children aged 8 years or younger were shown the same faces in pairs, without the numbers. These children were first shown faces 1 and 2. Children who chose the second face to describe their nausea intensity were then asked to consider faces 3 and 4. Face numbers range from 1 (no nausea) to 4 (worst nausea) (Faces adapted from Pharmacotherapy 26 (9):1223, 2006).

Determine terms used by the family when referring to nausea and vomiting.

To the child aged 4-8 years:

Have you ever thrown up (use family term) before?

If yes, how did your tummy feel just before you threw up (use family term)? _____ We call that feeling nausea or being nauseous. In your family you call that feeling _____.

If no, have you ever felt like you were going to throw up (use family term) but didn't?

If yes, how did your tummy feel then? _____ We call that feeling nausea or being nauseous. In your family you call that feeling _____.

Some children who get chemo feel nauseous (use family term) and some don't. Right now, which kind of child is more like you?

If child says no nausea, show faces 1 and 2.

Some children who get chemo feel no nausea (use family term) at all, like this face, and some feel a little bit nauseous (use family term), like this face. Point to each face at the appropriate time and use hands to emphasize "no nausea" and "a little bit". Which child is more like you right now?

If child says some nausea, show faces 3 and 4.

Some children who get chemo feel some nausea (use family term), like this face, and some feel a lot of nausea (use family term), like this face. Point to each face at the appropriate time and use hands to emphasize "some nausea" and "a lot". Which child is more like you right now?

To the child older than 8 years:

Have you ever thrown up (use family term) before?

If yes, how did you tummy/stomach feel just before you threw up (use family term)? _____ We call that feeling nausea or being nauseous. In your family you call that feeling _____.

If no, have you ever felt like you were going to throw up (use family term) but didn't?

If yes, how did your tummy/stomach feel then? _____ We call that feeling nausea or being nauseous. In your family you call that feeling _____.

Some children who get chemo feel nauseous (use family term) and some don't. These faces show children who feel no nausea at all, who feel a little bit nauseous, who feel even more nauseous, and who feel nauseous a whole lot. Point to each face at the appropriate time. Which face is more like you right now?

Figure 2. Scripts according to age for the Pediatric Nausea Assessment Tool administered to children who are receiving antioplastic agents (adapted from Pharmacotherapy 26 (9):1224, 2006)

Based on the results of the PeNAT tool, the multidisciplinary team should evaluate and make recommendations if necessary on optimizing antiemetic therapy.

A. NON-PHARMACOLOGIC MANAGEMENT

- Despite the advances in pharmacological management, standard pharmacological regimens may not fully alleviate symptoms of CINV in pediatric oncology patients. Investigating the adjuvant role of non-pharmacological interventions is an important consideration of antiemetic therapy. Non-pharmacological measures should be implemented in conjunction with pharmacological regimens to allow for the effective management of CINV. The use of non-pharmacological measures may not be appropriate for each patient, interventions should be implemented according to the individual patient's needs and circumstances.
  Some suggested non- pharmacological interventions may include; *music therapy, cognitive distraction, guided imagery, massage, acupressure and dietary concerns*. These non-pharmacologic interventions are beyond the scope of this guideline and will not be discussed except for dietary concerns which are discussed below.

Dietary Concerns:

- Advise the child not to eat for at least thirty minutes before chemotherapy starts
- Several small meals a day are better tolerated than three large meals

- Try to keep cooking smells or foods with strong odors away from the child
- Give plenty of fluids such as clear soups, flat pop, tea, jello or non-citrus fruit juice after episodes of vomiting
- Avoid fried, fatty or spicy foods
- Bland foods such as toast, crackers, potatoes, vegetables and easily digested meats (chicken) are often well tolerated
- Make mealtime as pleasant as possible for the child, for example serve food in an attractive way
- It may be beneficial to keep the child in a comfortable, relaxed, sitting position for at least 2 hours after eating
- Fresh air often helps reduce nausea
- After vomiting, allow time for child to recover, brush teeth and rinse mouth before offering any food
- When nausea/vomiting is severe, do not pressure the child to eat, they may acquire a learned aversion to certain foods
- Encourage napping times when nausea is expected

B. PHARMACOLOGIC MANAGEMENT:

Guiding principles of nausea and vomiting prevention and management:

1. Prevention of nausea and vomiting is very important and ever effort should be directed to making sure appropriate antiemetics are prescribed prior to the first cycle of chemotherapy. Evidence both anecdotal and from the literature indicates that if the patient receives suboptimal antiemetic management with the first cycle of chemotherapy subsequent cycles of chemotherapy become distressing based on this bad experience.
2. The success of antiemetic management is in optimizing therapy for every cycle of chemotherapy. Successful management of nausea and vomiting in this document is defined as no nausea and vomiting. If an antiemetic regimen was not completely effective with a cycle of chemotherapy then changes need to be made for subsequent cycles. This may include increasing doses of current agents or adding new agents or using a different regimen.
3. The emetogenic potential of the chemotherapy cycle is based on the emetogenic potential of the most emetogenic agent and management should be directed to that agent.

1. Antiemetic management

a. Initial Antiemetic Regimen (Chemo-naive patients)

Follow algorithms.

Note: For patients who are receiving multiple drugs known to prolong QT or who have a significant clinical history of QT prolongation: It is suggested that these patients receive baseline and continued ECG monitoring at the discretion of the treating physician. They should also receive oral ondansetron rather than intravenous and consideration should be given to giving ondansetron/granisetron with longer than standard intervals if the oral route is not possible.

b. Antiemetic management for subsequent cycles of chemotherapy and for patients who have experienced a lapse in cancer therapy (for example a relapse patient)

Follow algorithms if previous cycle was optimally managed. If antiemetic therapy was not effective in spite of appropriate management based on the algorithms, antiemetics doses should be maximized,

alternate antiemetics should also be considered or addition of a different class of antiemetic. This should be done in consultation with the pediatric hematology/oncology team.

2. Route of Administration for Antiemetic Agents

Whenever appropriate, antiemetics should be administered orally. If the oral route is not appropriate, antiemetic should be administered intravenously.

3. Duration of Antiemetic Administration

- Continue antiemetics "around the clock" not PRN for at least 48 hours after the end of chemotherapy.
- Dexamethasone if used should be discontinued 24 hours after the end of the chemotherapy.
- Antiemetics may need to be continued as needed (PRN).

4. Management of Antiemetic Failure

Breakthrough nausea and vomiting occurs when the patient experiences 2 vomits or retches within a 24 hour period, or experiences greater than or equal to 3 hours of significant nausea per day, such that it affects the patient's level of activity.

Refractory nausea and vomiting occurs when antiemetic regimens stop working this may happen after a few cycles of chemotherapy.

The following is a guide and management is not limited to these options.

Breakthrough nausea and vomiting treatment options:

a) Add dimenhydrinate 1 mg/kg/dose (maximum 50 mg/dose) IV/PO q4h prn. OR
b) Add lorazepam 0.025-0.05 mg/kg/dose (maximum 2 mg/dose) IV/PO/SL q6h prn
c) Increase the dose of current antiemetics but do not exceed maximum doses, starting with the 5HT3 antagonist.
d) Add an antiemetic from another class. Ex. Consider the addition of scopolamine patch (1 patch prior to chemotherapy for children greater than or equal to 18 kg and ½ patch for children less than 18 kg – tape half of patch do not cut). Replace patch every 3 days. OR consider the use of chlorpromazine (monitor hypotension and sedation). OR consider second generation 5HT3 antagonists, ex. palonosetron.

Refractory nausea and vomiting treatment options:

a) Modify antiemetic regimen for next cycle of chemotherapy by changing the combination of agents and/or maximizing doses.
b) Consider the addition of dexamethasone if not already incorporated and not contraindicated.
c) Consider the addition of aprepitant if not already incorporated and not contraindicated.
d) If patient fails on 2 consecutive cycles, substitute granisetron (40 micrograms/kg/dose (maximum 1 mg/dose) PO q12h or 40 micrograms/kg/dose (maximum 1 mg/dose) IV once daily) for ondansetron.
e) Consider second generation 5HT3 antagonists, ex. palonosetron if granisetron ineffective especially in cases of refractory delayed nausea and vomiting.

5. Other considerations:

a) A multidisciplinary approach to managing CINV will assist in providing appropriate supportive care and effective antiemetic regimens to the pediatric oncology patient.

b) Current literature supports the use of ginger supplementation to manage general nausea and vomiting, however ginger is not recommended for use in the pediatric oncology population due to unknown effects on coagulation.
c) Poorly controlled CINV can result in dehydration, electrolyte imbalance, anorexia and, fatigue.
d) Antiemetic therapies should be routinely administered during chemotherapy administration known to induce nausea and vomiting, not just PRN when patients develop symptoms of nausea.
e) If a patient is being discharged with antiemetic medications, the patient and/or caregivers should be given instructions on management of antiemetic regimens at home, prior to discharge.

The following 3 algorithms provide tools for the healthcare provider to determine how to manage chemotherapy induced nausea and vomiting (CINV) in children with cancer. The algorithms have been adapted from the 2012 POGO guidelines for the Prevention of Acute Nausea and Vomiting due to Antineoplastic Medication.

- **APPHON/ROHPPA Prevention and management of CINV in Pediatric Cancer Patients - Low and Minimal Emetogenic Risk**
- **APPHON/ROHPPA - Prevention and management of CINV in Pediatric Cancer Patients - Moderate Emetogenic Risk**
- **APPHON/ROHPPA - Prevention and management of CINV in Pediatric Cancer Patients – High Emetogenic Risk**

References:

L. Lee Dupuis, M.Sc.Phm., FCSHP, Anna Taddio, Ph.D., Elizabeth N. Kerr, Ph.D., Andrea Kelly, B.Sc.Phm., and Linda MacKeigan, Ph.D. Development and Validation of the Pediatric Nausea Assessment Tool for Use in Children Receiving Antineoplastic Agents. Pharmacotherapy, Volume 26, Number 9, 2006.

Dupuis LL, Boodhan S, Holdsworth M, Robinson PD, Hain R, Portwine C, O'Shaughnessy E and Sung L. Guideline for the Prevention of Acute Nausea and Vomiting due to Antineoplastic Medication in Pediatric Cancer Patients. Pediatric Oncology Group of Ontario; Toronto. 2012.

Dupuis LL, Boodhan S, Sung L, Holdsworth M, Robinson PD, Hain R, Portwine C, McCarthy P and Sung L. Guideline for classification of the acute emetogenic potential of antineoplastic medication in pediatric cancer patients. Pediatric Oncology Group of Ontario; Toronto. 2010.

Dupuis LL, Robinson PD, Boodhan S, Holdsworth M, Portwine C, Gibson P, Phillips R, Maan C, Stefin N and Sung L. Guideline for the Prevention and Treatment of Anticipatory Nausea and Vomiting due to Chemotherapy in Pediatric Cancer Patients. Pediatric Oncology Group of Ontario; Toronto. 2014.

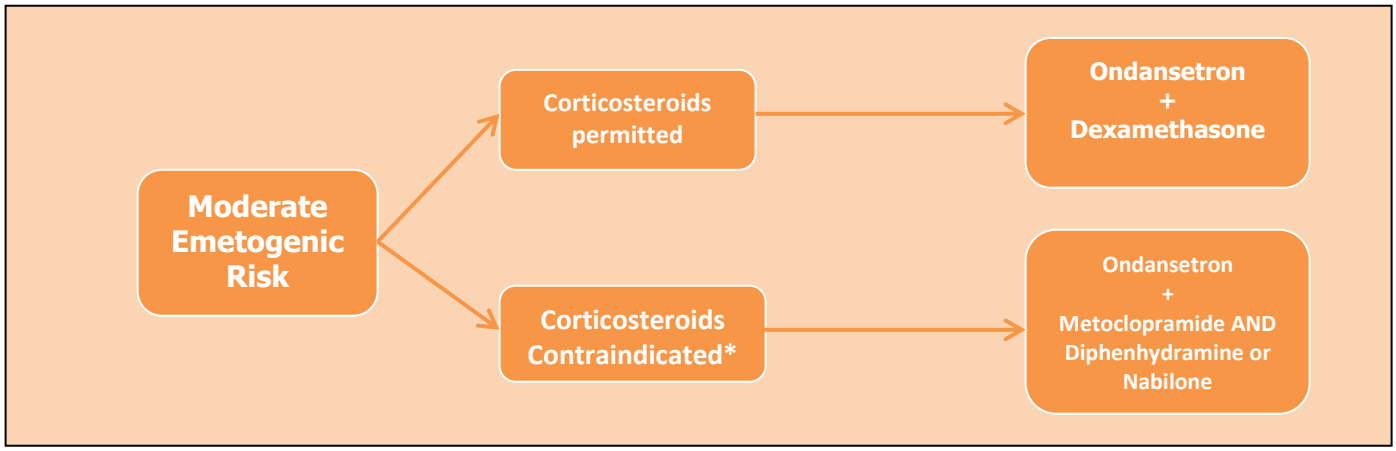
APPHON/ROHPPA Prevention and management of CINV in Pediatric Cancer Patients Low and Minimal Emetogenic Risk (adapted from POGO 2012)

Antineoplastic Agents with LOW Emetic Risk 10% to <30% frequency of emesis in absence of prophylaxis	
Single agent antineoplastic therapy	
Cytarabine ≤200 mg/m^2 Cytarabine intrathecal Docetaxel Doxorubicin (liposomal) Etoposide Fludarabine (oral) 5-Fluorouracil Gemcitabine Methotrexate >50 mg/m^2 to <250 mg/m^2	Mitomycin Mitoxantrone Nilotinib Paclitaxel Paclitaxel-albumin Pemetrexed Teniposide Topotecan Vorinostat
Multiple agent antineoplastic therapy	
Multi-day antineoplastic therapy	
Emetogenicity is classified based on the most highly emetogenic agent on each day of therapy.	

Antiemetic Dosage Recommendations for Children receiving LOW Emetic Risk Antineoplastic Therapy	
Drug	**Dose**
Ondansetron	10 mg/m^2/dose OR (0.2-0.3 mg/kg/dose) OR Maximum 16 mg/dose IV (See exemptions under antiemetic management section) 24 mg/dose PO pre-therapy x 1 Breakthrough nausea and vomiting: Dimenhydrinate – 1 mg/kg (maximum 50 mg/dose) IV/PO q4h as needed OR lorazepam 0.025-0.05 mg/kg/dose (max 2 mg/dose) IV/PO/SL q6h as needed. If ineffective see Management of Antiemetic Failure. Anticipatory nausea and vomiting: Lorazepam - 0.04-0.08 mg/kg/dose (max 2 mg/dose) the night before chemotherapy and repeat a dose just prior to chemotherapy.

Antineoplastic Agents with MINIMAL Emetic Risk <10% frequency of emesis in absence of prophylaxis		
Single agent antineoplastic therapy		
Alemtuzumab Alpha interferon Asparaginase (IM or IV) Bevacizumab Bleomycin Bortezomib Cetuximab Chlorambucil (oral) Cladribine Dasatinib Decitabine	Erlotinib Fludarabine Gefitinib Gemtuzumab ozogamicin Hydroxyurea (oral) Lapatinib Lenalidomide Melphalan (oral low-dose) Mercaptopurine (oral) Methotrexate ≤50 mg/m^2 Nelarabine Panitumumab Pentostatin	Rituximab Sorafenib Sunitinib Temsirolimus Thalidomide Thioguanine (oral) Trastuzumab Valrubicin Vinblastine Vincristine Vindesine Vinorelbine
For multiple agent and multi-day antineoplastic therapy – Please refer to recommendations in Low emetic risk table.		

APPHON/ROHPPA - Prevention and management of CINV in Pediatric Cancer Patients Moderate Emetogenic Risk (adapted from POGO 2012)



Antineoplastic Agents with MODERATE Emetic Risk 30-90% frequency of emesis in absence of prophylaxis
Single agent antineoplastic therapy
Arsenic trioxide Azacitidine Bendamustine Carmustine ≤250 mg/m^2 Clofarabine Cyclophosphamide <1 g/m^2 Cyclophosphamide (oral) Cytarabine >200 mg to <3 g/m^2 Daunorubicin Doxorubicin Epirubicin Etoposide (oral) Idarubicin Ifosfamide Imatinib (oral) Irinotecan Lomustine Methotrexate ≥250 mg to <12 g/m^2 Oxaliplatin >75 mg/m^2 Temozolomide (oral) Vinorelbine (oral)
Multiple agent antineoplastic therapy
With the exceptions listed under high emetic risk, emetogenicity is classified based on the most highly emetogenic agent.
Multi-day antineoplastic therapy
Emetogenicity is classified based on the most highly emetogenic agent on each day of therapy.

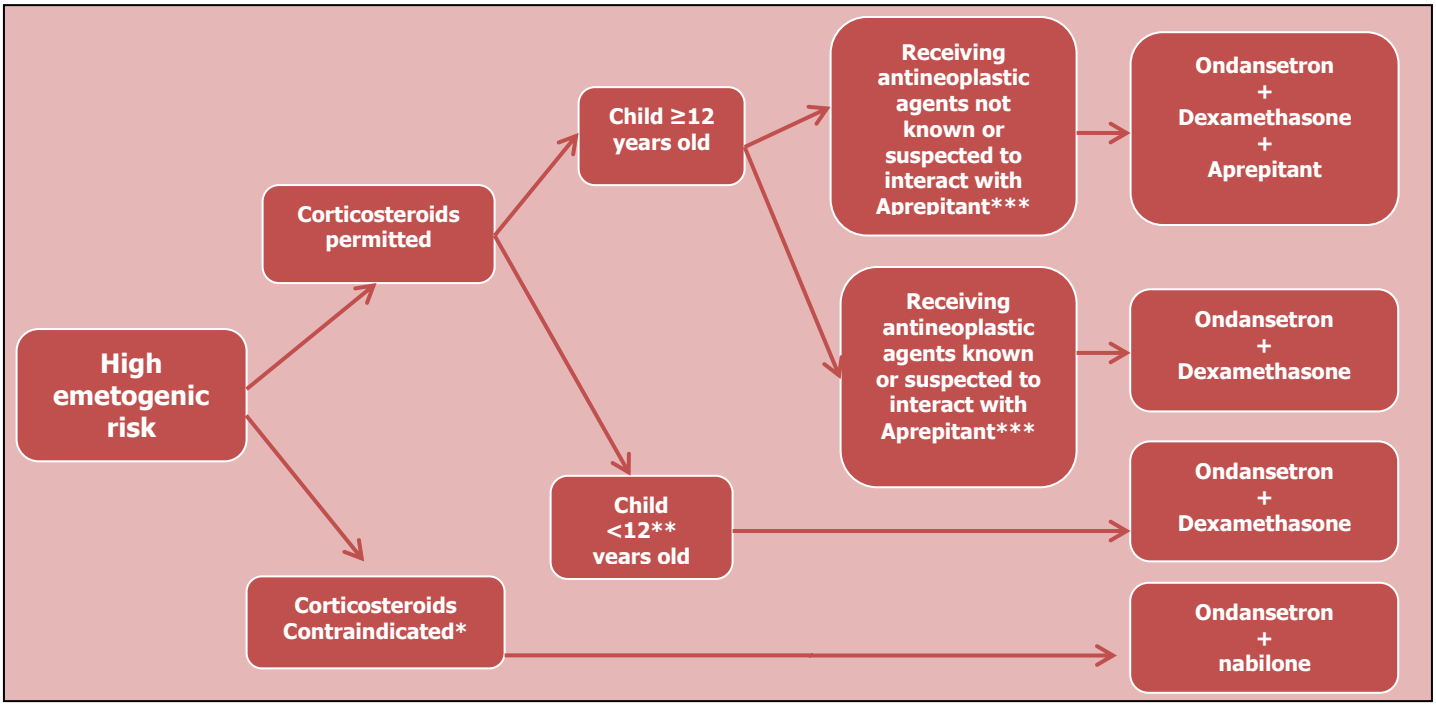
Antiemetic Dosage Recommendations for Children receiving MODERATELY Emetogenic Antineoplastic Therapy	
Drug	**Dose**
Dexamethasone	≤0.6 m^2: 2 mg/dose IV/PO q12 hr >0.6m^2: 4 mg/dose IV/PO q12hr
Ondansetron	(0.15 mg/kg/dose; maximum 8 mg/dose) IV/PO pre-therapy x 1 and then q12h
Metoclopramide	1 mg/kg/dose (max 40 mg/dose) Give diphenhydramine 1 mg/kg/dose (max 50 mg/dose) concurrently with metoclopramide pre therapy and then q6h.
Nabilone	<18 kg: 0.5 mg/dose PO twice daily 18 to 30 kg: 1 mg/dose PO twice daily >30 kg: 1 mg/dose PO three times daily Maximum: 0.06 mg/kg/day

* Corticosteroid contraindicated in CNS tumours, AML and any study that prohibits their use as an antiemetic.

Breakthrough nausea and vomiting: Dimenhydrinate - 1 mg/kg IV/PO q4h as needed
OR lorazepam 0.025-0.05 mg/kg/dose (max 2 mg/dose) IV/PO/SL q6h as needed.
Anticipatory nausea and vomiting: Lorazepam - 0.04-0.08 mg/kg/dose (max 2 mg/dose) the night before chemotherapy and repeat a dose just prior to chemotherapy.

Continue antiemetics around the clock for at least 48 hours after the end of chemotherapy then may switch to as needed.
Dexamethasone should be discontinued 1 day after chemotherapy is complete.
If ineffective see Management of Antiemetic Failure.

APPHON/ROHPPA - Prevention and management of CINV in Pediatric Cancer Patients High Emetogenic Risk (adapted from POGO 2012)



Antineoplastic Agents with HIGH Emetic Risk >90% frequency of emesis in absence of prophylaxis	
Single agent antineoplastic therapy	
Carboplatin Carmustine >250 mg/m^2 Cisplatin Cyclophosphamide ≥1 g/m^2 Cytarabine 3 g/m^2/dose Dacarbazine	Dactinomycin Methotrexate ≥12 g/m^2 Procarbazine (oral)
Multiple agent antineoplastic therapy	
With the exceptions listed below, emetogenicity is classified based on the most highly emetogenic agent. The following are also classified as high emetic risk: Cyclophosphamide + anthracycline Cyclophosphamide + doxorubicin Cyclophosphamide + epirubicin Cyclophosphamide + etoposide Cytarabine 150-200 mg/m^2 + daunorubicin Cytarabine 300 mg/m^2 + etoposide Doxorubicin + ifosfamide Doxorubicin + methotrexate 5 g/m^2 Etoposide + ifosfamide	
Multi-day antineoplastic therapy	
Emetogenicity is classified based on the most highly emetogenic agent on each day of therapy.	

Antiemetic Dosage Recommendations for Children receiving HIGHLY Emetogenic Antineoplastic Therapy	
Drug	**Dose**
Aprepitant	Day 1: 125 mg PO x 1 Days 2 and 3: 80 mg PO once daily
Dexamethasone	6 mg/m^2/dose IV/PO once daily may increase to BID (maximum 20 mg/day) If given concurrently with aprepitant, reduce dexamethasone dose by half
Ondansetron	0.15-0.2 mg/kg/dose (max 8 mg/dose) IV/PO Pre-therapy x 1 and then q8hr
Nabilone	<18 kg: 0.5 mg/dose PO twice daily 18 to 30 kg: 1 mg/dose PO twice daily >30 kg: 1 mg/dose PO three times daily Maximum: 0.06 mg/kg/day

***Drugs that interact with aprepitant
Bortezomib
Busulfan
Cyclophosphamide
Dasatinib
Daunorubicin
Docetaxel
Doxorubicin
Etoposide
Imatinib
Ifosfamide
Irinotecan
Lapatinib
Melphelan
Nilotinib
Paclitaxel
Sorafenib
Sunitinib
Tamoxifen
Teniposide
Thiotepa
Vinblastine
Vincristine
Vinorelbine

* Corticosteroid contraindicated in CNS tumours, AML and any study that prohibits their use as an antiemetic.

**For children less than 12 years may consider the use of aprepitant check with clinical oncology pharmacist for dosing.

***When prescribing aprepitant always check with the pediatric oncology clinical pharmacist for interactions with chemotherapy agents. The list provided above may not include newly identified interacting drugs.

Breakthrough nausea and vomiting: Dimenhydrinate - 1 mg/kg IV/PO q4h as needed OR lorazepam 0.025-0.05 mg/kg/dose (max 2 mg/dose) IV/PO/SL q6h prn.

Anticipatory nausea and vomiting: Lorazepam - 0.04-0.08 mg/kg/dose (max 4 mg/dose) the night before chemotherapy and repeat a dose just prior to chemotherapy for anticipatory nausea and vomiting

Continue antiemetics around the clock for at least 48 hours after the end of chemotherapy then may switch to as needed. Dexamethasone should be discontinued 1 day after chemotherapy is complete.

If ineffective see Management of Antiemetic Failure.