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

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

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.

Unofficial document if printed. To ensure that this printed is the latest version, please check website http://www.apphon-rohppa.com.

The recommendations in this guideline are adapted from the POGO guidelines **Guideline for the prevention of acute chemotherapy-induced nausea and vomiting in pediatric cancer patients (February 2017)** and **Guideline for the prevention and treatment of anticipatory nausea and vomiting due to chemotherapy in pediatric cancer patients (March 2021)** and from **Classification of the acute emetogenicity of chemotherapy in pediatric patients: A clinical practice guideline (January 2019).** Where pediatric evidence was not available **the National Comprehensive Cancer Network NCCN Antiemesis guideline (2020)** and **Multinational Association of Supportive Care in Cancer (MASCC/ESMO) antiemetic guideline updated 2019** and **the American Society of Clinical Oncology ASCO antiemetics guideline (Hesketh et al; 2020)** were used to make recommendation regarding emetogenicity of commonly used chemotherapy agents in pediatrics. Where discrepancies occurred between these documents with respect to the level of emetogenicity of the agents, the higher emetogenic potential was used.
The full version along with the systematic reviews for these guidelines can be found at:

- Pediatric Oncology Group of Ontario (POGO) https://www.pogo.ca/healthcare/practiceguidelines/chemotherapy-induced-nausea-and-vomiting-cinv/
- National Comprehensive Cancer Network (NCCN) https://www.nccn.org/guidelines.
- Multinational Association of Supportive Care in Cancer (MASCC) www.macss.org.
- American Society of Clinical Oncology (ASCO) guideline citation (Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: ASCO Guideline Update. *JCO* 2020;38(24):2782-2797.

The APPHON/ROHPPA guideline utilized the POGO 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 Pediatric Oncology Group of Ontario (POGO) has classified chemotherapy agents based on their emetogenic potential and this APPHON guideline will follow the POGO classifications. 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 guideline will include the management of acute, delayed, anticipatory, breakthrough and refractory CINV in one document to aid health care providers in the management of CINV in the Atlantic Provinces.

The reason for the APPHON adaptation of the POGO guideline for the prevention of acute nausea and vomiting and not adoption of the guideline was because dosing of dexamethasone differed (Appendix 1), and several commonly used chemotherapy agents were not included in the POGO guideline. 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.

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DEFINITIONS

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

- ACUTE: most commonly begins within 1-2 hours of chemotherapy administration and peeks around 4-6 hours and resolves within 24 hours.
- DELAYED: occurs after 24 hours and usually within 7 days after chemotherapy administration.
- 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 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.

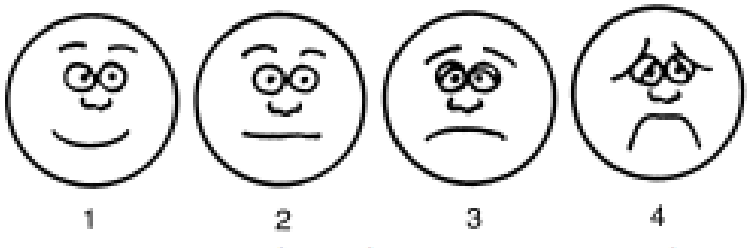

Figure 1.0 Faces used for administration of the Pediatric Nausea Assessment Tool to children older than 8 years. Children aged 8 years or younger were shown the same faces in pairs, without the numbers. These children were first shown faces 1 and 2. Children who chose the second face to describe their 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 your 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 2.0 Scripts according to age for the Pediatric Nausea Assessment Tool administered to children who are receiving antineoplastic 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.

I. 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 Interventions:

- 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
- Offering food while it is cold may help as cold food smells less
- Give plenty of fluids such as water, rehydration solutions/popsicles, clear soups, flat pop, tea, jello, or non-citrus fruit juice, after episodes of vomiting. Small volumes frequently are often better tolerated than large volumes.
- Avoid fried, fatty or spicy foods
- Bland foods such as toast, crackers, potatoes, rice, vegetables, and easily digested meats (chicken) are often better 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. If unable to go outside or open a window the use of a fan may be of benefit.
- After vomiting, allow time for child to recover, brush teeth and rinse mouth, before offering any food
- When nausea/vomiting is present, do not pressure the child to eat, they may acquire a learned aversion to certain foods
- Encourage napping times when nausea is expected.

II. PHARMACOLOGIC MANAGEMENT:

Guiding principles of nausea and vomiting prevention and management:

A. Prevention of nausea and vomiting is very important, and every 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 and possibly more difficult to control.

B. 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.

C. The emetogenic potential of the chemotherapy cycle dictates the approach to management of CINV for each chemotherapy cycle is based on the agent with the highest emetogenic potential.

1. <u>Antiemetic Management of Chemotherapy Induced Nausea and Vomiting</u>

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 ondansetron orally rather than intravenously, and consideration should be given to give a 5-HT3 antagonist (e.g., ondansetron/granisetron) with longer than standard intervals if the oral route is not possible. Palonosetron does not have a clinically significant effect on the QTc interval.

The ***acute phase*** of CINV that occurs within the first 24 hours after chemotherapy administration generates free radicals that induce serotonin (5-HT) release which initiates the vomiting reflex. 5-HT3 antagonists (such as ondansetron, granisetron and palonosetron) are very effective for this phase of AINV. The 5-HT3 antagonist antiemetics can result in serotonin syndrome if used with other agents that increase serotonin levels (use these drug combinations with caution).

The ***delayed phase*** of CINV that occurs greater than 24 hours after the start of chemotherapy and is associated with certain chemotherapy agents (e.g., cisplatin, carboplatin $\geq$ 600 mg/m^2/dose, doxorubicin $\geq$ 40 mg/m^2/dose, ifosfamide and cyclophosphamide).

Agents prescribed for delayed phase nausea and vomiting:

- This stage occurs due to activation of substance P and therefore is managed with upfront use of Neurokinin-1 receptor antagonists (NK-1 RA) (e.g., aprepitant and fosaprepitant) that block substance P. Consult a clinical pharmacist or oncologist for any drug interactions and contraindications to the use of NK-1 RAs.
- Dexamethasone (corticosteroid) is an efficacious antiemetic for delayed phase nausea and vomiting and should be prescribed if not contraindicated.
- Palonosetron is more efficacious for delayed CINV than other 5-HT3 antagonists as it has a longer half-life (40 hours vs 3 hours).
- Olanzapine is helpful in reducing both acute and delayed phase nausea and vomiting as it blocks both serotonin and dopamine receptors.

B. Antiemetic management for subsequent cycles of chemotherapy and for patients who have been without treatment for an extended interval (for example a relapse patient)

Follow algorithms if previous cycle was optimally managed. If antiemetic therapy was not effective despite appropriate management based on the algorithms, doses should be maximized, alternate agents 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, intravenous administration is recommended.

3. Duration of Antiemetic Administration

- Continue antiemetics "around the clock", not PRN, for at least 24 hours after the end of chemotherapy.
- Dexamethasone, if used, should be discontinued 24 hours after the end of the chemotherapy. If the patient is receiving multi-day chemotherapy likely to cause delayed nausea and vomiting dexamethasone should be continued for 2 to 3 days after chemotherapy.
- Neurokinin-1 receptor antagonists (e.g., aprepitant and fosaprepitant) should be prescribed for multi-day chemotherapy regimens (unless contraindicated) expected to cause delayed nausea and vomiting for the duration of the chemotherapy exposure. Typical duration is 3 days but up to 7 days may be considered. Dosing should be the higher dose on day 1 followed by the lower dose days 2-7 (e.g., 125 mg day 1 followed by 80 mg day 2-7). Data are not available on extended dosing of fosaprepitant.
- Antiemetics may need to be continued as needed (PRN).

4. Management of Antiemetic Failure

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

A) Breakthrough nausea and vomiting treatment recommendations: (see Algorithm 7)

Breakthrough CINV is defined as nausea and/or vomiting presumed to be attributable to chemotherapy and with no other pathological cause that occurs during the acute or delayed phase, despite CINV prophylaxis as per these guidelines. Breakthrough nausea and vomiting occurs when the patient experiences 2 or more vomits or retches within a 24-hour period, or experiences 3 hours, or more, of significant nausea per day, such that it affects the patient's level of activity.

- Breakthrough emesis presents a difficult situation, as correction of ongoing nausea and vomiting is often challenging to reverse. It is generally far easier to prevent nausea and vomiting than it is to treat it.
- The general principle of breakthrough treatment is to give an additional agent from a different drug class. The choice of agent should be based on assessment of the current prevention strategies used. Some patients may require several agents utilizing differing mechanisms of action.
- Scheduled administration, rather than PRN dosing, is strongly recommended until the nausea and/or vomiting has resolved.
- If the child is receiving highly emetogenic chemotherapy we suggest the addition of olanzapine* as a first choice if the drug is not contraindicated.
- If olanzapine is contraindicated then multiple concurrent agents, perhaps in alternating schedules or by alternating routes, may be necessary. Dopamine antagonists (e.g., methotrimeprazine*), corticosteroids, and agents such as dimenhydrinate, lorazepam and nabilone may be required.
- A switch to a different 5-HT3 antagonist. Although not likely to be effective, anecdotal data suggest it may sometimes improve outcome based on slight variances in the pharmacokinetic and pharmacodynamic parameters (PK/PDs) between ondansetron and granisetron. Palonosetron should be considered for any delayed nausea and vomiting.
- Ensure adequate hydration or fluid repletion and correct any possible electrolyte abnormalities.
- Prior to the next cycle of chemotherapy, the patient should be reassessed, with attention given to various possible non-cancer related reasons for the breakthrough nausea and vomiting including, but not limited to, electrolyte abnormalities, tumor infiltration into the bowel or brain, abdominal/pelvic radiation, and other comorbidities.
- Consider the addition of an H2 antagonist (e.g., famotidine) or a proton pump inhibitor for acid suppression which can cause nausea (assess for drug interactions).

*Given the possibility of extrapyramidal reactions with olanzapine and methotrimeprazine, the risks and benefits of their use should be weighed carefully, and co-administration of prophylaxis aimed at preventing extrapyramidal symptoms (EPS) should be considered (e.g., diphenhydramine 1-2 mg/kg/dose (max 50 mg/dose) may repeat in 30 minutes, subsequent

doses if needed 1 mg/kg/dose q6h prn). Patients and families should also be educated about the possible occurrence of EPS. These antipsychotic antiemetics should be used with caution in children who have known psychiatric diagnosis.

B) Refractory nausea and vomiting treatment recommendations: (see Algorithm 8)

Refractory CINV is defined as nausea and/or vomiting presumed to be attributable to chemotherapy, and with no other pathological cause which occurs during the acute or delayed phase despite appropriate CINV prophylaxis in patients who have experienced breakthrough CINV in a previous chemotherapy block. Refractory nausea and vomiting occur when antiemetic regimens stop working. This may happen after a few cycles of chemotherapy.

1. For children receiving acute CINV prophylaxis recommended for minimally, low, or moderately emetogenic chemotherapy, clinicians should upgrade or escalate the acute CINV prophylaxis provided to that recommended for chemotherapy of the next higher level of emetogenic risk.

2. For children receiving acute CINV prophylaxis recommended for highly emetogenic chemotherapy, we suggest that the 5-HT3 antagonist given for CINV prophylaxis be changed from ondansetron or granisetron to palonosetron.

3. For children experiencing refractory CINV despite initiation of above recommendations and who have not previously received aprepitant/fosaprepitant, we suggest that the addition of aprepitant/fosaprepitant to acute CINV prophylaxis be considered if it is not contraindicated due to drug interactions (see drug interaction section).

4. For children experiencing refractory CINV despite initiation of the above recommendations, we suggest that one of the following interventions be added to the CINV prophylaxis provided:

    - Interventions that were employed successfully for the treatment of breakthrough CINV in previous treatment blocks (olanzapine, methotrimeprazine, lorazepam or nabilone) **OR**
    - Stimulation of Nei Gaun (P6) by means of acupressure or electro acupuncture (please consult an acupuncturist for accurate placement and a pediatric oncologist to determine safety of acupuncture for the patient).

C) Delayed nausea and vomiting treatment recommendations: (See Algorithm 9)

Delayed nausea and vomiting occur after the first 24 hours after chemotherapy and usually within 7 days.

If delayed nausea and vomiting occurs during a cycle immediately consider:

1. Adding a corticosteroid if not contraindicated (avoid in AML, brain tumor patients and patients with unhealed wounds and any protocol that steroids are contraindicated). Continue for 24 hours after the nausea and vomiting has resolved.
2. If adding corticosteroids alone fails, substitute ondansetron with palonosetron with olanzapine (unless contraindicated) OR aprepitant/fosaprepitant (unless contraindicated).
3. If corticosteroids are contraindicated give palonosetron with olanzapine (unless contraindicated) OR with aprepitant/fosaprepitant (unless contraindicated).

For patients who have experienced delayed nausea and vomiting in a previous cycle consider the following for addition of antiemetics to upfront CINV prophylaxis for subsequent cycles:

1. Addition of aprepitant/fosaprepitant upfront, if not contraindicated (consult a clinical pharmacist or oncologist for any drug interactions and contraindications)
2. Addition of corticosteroid, if not contraindicated.
3. Switch 5-HT3 antagonist from ondansetron/granisetron to palonosetron.
4. Consider the addition of olanzapine, if not contraindicated.

D) Anticipatory nausea and vomiting treatment recommendations: (See Algorithm 10)

Anticipatory nausea and vomiting occur before the patient receives chemotherapy and is thought to be associated with previously poorly controlled nausea and vomiting. If patient is anxious prior to start of chemotherapy or experiences anxiety during chemotherapy add lorazepam and start the evening before the start of chemotherapy. Behavioral intervention may also be helpful for a child who is experiencing anxiety.

E) Drug interactions of chemotherapy agents with aprepitant/fosaprepitant: (Consult an oncology pharmacist or oncologist for information on drug interactions).

- Aprepitant is a neurokinin-1 antagonist along with its intravenous prodrug fosaprepitant.
- Aprepitant/fosaprepitant are substrates of CYP3A4 and dose dependent inhibitors and inducers of CYP3A4. This means that aprepitant/fosaprepitant can increase the concentration of chemotherapy drugs that are substrates of CYP3A4 and later increase clearance of these agents which can result in both increased toxicity and decreased efficacy of the chemotherapy agents.
- CYP3A4 inhibitors such as aprepitant/fosaprepitant may also reduce the conversion of a prodrug to its active form.

- Young children are at increased risk for these interactions as the concentration of CYP3A4 only reaches about 30% at 1 year of age.
- Data are limited on the clinical significance of these interactions.
- The drug interactions are dose dependent and therefore less significant with one-time doses of aprepitant/fosaprepitant. Also, fosaprepitant (the intravenous form) is a weaker inhibitor of CYP3A4 as it avoids first pass metabolism and as such reduces inhibition of CYP3A4 in the liver and the gastrointestinal tract, and thus any interaction will likely be less significant.
- If using aprepitant/fosaprepitant with dexamethasone, ensure the dose of dexamethasone is halved due the doubling of its serum concentration by aprepitant.

The following is a list of chemotherapy and supportive care agents that are commonly used in pediatric protocols for which limited data are available to assess the risk vs benefit of combined use with aprepitant/fosaprepitatant:

- *Ifosfamide*: avoid this combination due to increase in serum concentrations and CNS toxicity namely encephalopathy (data available form case reports). Aprepitant/fosaprepitant may also increase clearance of ifosfamide by up to 60%.
- *Cyclophosphamide*: Use with caution as some reports of increased serum concentrations and prevention of conversion of this prodrug to its active form.
- *Anthracyclines*: Use with caution as may increase the serum concentration of and result in more severe cardiac toxicity.
- *Vinca alkaloids (i.e., vincristine, vinblastine, vinorelbine*): Use with caution as may increase the serum concentration and result in increased peripheral neuropathy.
- *Etoposide*: Use with caution due to potential increase in serum concentration and increased AEs.
- *Tyrosine kinase inhibitors (e.g., imatinib, dasatinib etc*): Use with caution due to potential increase in serum concentration and increased AEs.
- *Irinotecan*: Use with caution as some reports of increased serum concentrations and prevention of conversion of this prodrug to its active form.
- *Benzodiazepines*: Use with caution due to potential increase in serum concentration. Monitor for CNS toxicity, increase in somnolence.
- *Azoles (i*.e., fluconazole, voriconazole): Use with caution as may increase the serum concentration of aprepitant/fosaprepitant (consider lowering the dose of aprepitant/fosaprepitant).
- *Glucocorticosteriods* (i.e., dexamethasone): Increased serum concentration of dexamethasone. If using dexamethasone with aprepitant/fosaprepitant as an antiemetic reduce the dose of dexamethasone in half.

- Review the appropriateness of use of aprepitant and fosaprepitant with any chemotherapy agent that is a CYP3A4 substrate.

F) Radiation induced nausea and vomiting:

- High emetogenic potential: Total body irradiation
- Moderate emetogenic potential: Upper abdomen, craniospinal
- Low emetogenic potential: Cranium, head and neck, thorax region, pelvis
- Minimal emetogenic potential: extremities, breast

For patients who receive radiation to the upper abdomen or craniospinal radiation should receive a dose of either ondansetron or granisetron +/- dexamethasone pretreatment and up to twice daily on radiation days. For breakthrough radiation induced nausea and vomiting patients can be treated with another class of antiemetic like anticancer agent-induced emesis.

In concomitant radio-chemotherapy, the antiemetic prophylaxis is according to the chemotherapy related antiemetic guidelines of the corresponding risk category unless the risk of emesis is higher with radiotherapy than chemotherapy.
Radiation somnolence syndrome is an early to delayed adverse effect of cranial radiation which presents as extreme lethargy and signs of increased intracranial pressure including nausea and vomiting. It may be difficult to distinguish this from CINV both acute and delayed. Diagnosis and management of radiation somnolence syndrome should be discussed with the patient's oncologist.

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) Poorly controlled CINV can result in dehydration, electrolyte imbalance, anorexia, and fatigue.
C) Antiemetic therapies should be routinely administered during chemotherapy administration known to induce nausea and vomiting, not just PRN when patients develop symptoms of nausea.
D) 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.

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Algorithm 1: APPHON/ROHPPA
Prevention of Acute CINV in Pediatric Cancer Patients Receiving ORAL Chemotherapy Agents MINIMAL to LOW Emetogenic Risk

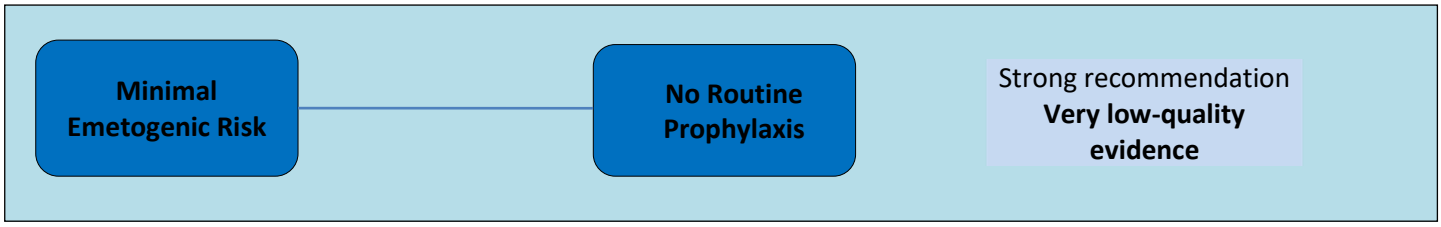
Minimal to Low Emetogenic Risk	Graniestron Ondansetron	Strong recommendation Low quality evidence

Antineoplastic Agents with MINIMAL to Low Emetic Risk <10% frequency of emesis in absence of prophylaxis		Antiemetic Dosage Recommendations for Children receiving Minimal to LOW Emetic Risk Antineoplastic Therapy		
Single agent antineoplastic therapy		**Drug**	**Dose**	**Grade**
Dasatinib **Decitabine** **Erlotinib** **Everolimus** **Fludarabine** **Gefitinib** **Gilteritinib** **Hydroxyurea** **Lapatinib** **Larotrectinib** **Lenalidomide** **Lorlatinib** **Mercaptopurine** **Methotrexate** **Nilotinib**	**Pazopanib** **Panotinib** **Regorafenib** **Ruxolitinib** **Sorafenib** **Selumetinib** **Sunitinib** **Thalidomide** **Thioguanine** **Topotecan** **Trametinib** **Tretinoin** **Venetoclax** **Vorinostat**	**Granisetron**	**Intravenous** 0.04 mg/kg IV daily **Maximum:** 3 mg/dose **Oral** *Round all calculated doses to nearest 1/2 tablet portion (0.5 mg increments)* 0.04 mg/kg PO BID **Maximum:** 2 mg/dose	**Strong recommendation** **Low quality evidence**
		Ondansetron	**0.1 - 0.2 mg/kg/dose (max 8 mg/dose)** **IV/PO pre-chemotherapy prn x 1**	**Strong recommendation** **Low quality evidence**
Multiple Agent/Multi-Day Antineoplastic Therapy **Emetogenicity is classified based on the most highly emetogenic agent on each day of therapy.**				

Algorithm 2: APPHON/ROHPPA
Prevention of Acute CINV in Pediatric Cancer Patients Receiving ORAL Chemotherapy
Agents with MODERATE to HIGH Emetogenic Risk

Antineoplastic Agents with MODERATE TO HIGH Emetic Risk ≥ 30% frequency of emesis in absence of prophylaxis	Antiemetic Dosage Recommendations for Children receiving MODERATE to HIGH Emetic Risk Antineoplastic Therapy		
Single agent antineoplastic therapy	**Drug**	**Dose**	**Grade**
Crizotinib **Cyclophosphamide** **Dabrafenib** **Dacarbazine** **Etoposide** **Imatinib** **Lomustine** **Procarbazine** **Temozolomide**	**Granisetron**	**Intravenous** 0.04 mg/kg IV daily **Maximum:** 3 mg/dose **Oral** *Round all calculated doses to nearest 1/2 tablet portion (0.5 mg increments)* 0.04 mg/kg PO BID **Maximum:** 2 mg/dose	**Strong recommendation** **Low quality evidence**
	Ondansetron	**0.1 - 0.2 mg/kg/dose (max 8 mg/dose) IV/PO pre-chemotherapy x 1 and up to TID prn**	**Strong recommendation** **Low quality evidence**
Multiple Agent/Multi-Day Antineoplastic Therapy **Emetogenicity is classified based on the most highly emetogenic agent on each day of therapy.**			

Algorithm 3: APPHON/ROHPPA Prevention of Acute CINV in Pediatric Cancer Patients with MINIMAL Emetogenic Risk (Parenteral Route)



Antineoplastic Agents with MINIMAL Emetic Risk <10% frequency of emesis in absence of prophylaxis
Single agent antineoplastic therapy
Alemtuzumab **Asparaginase (Erwinia) IM** **Asparaginase (Pegylated) IV/IM** **Bevacizumab** **Bleomycin** **Cladribine** **Emapalumab** **Fludarabine** **Lipsosomal doxorubicin IV ≤ 50mg/m^2/dose** **Methotrexate PO/SC ≤ 10mg/m^2/dose** **Nivolumab** **Pembrolizumab** **Rituximab** **Trastuzumab** **Vinblastine** **Vincristine** **Vinorelbine**
For multiple agent and multi-day antineoplastic therapy – Please refer to recommendations in Low emetic risk table.

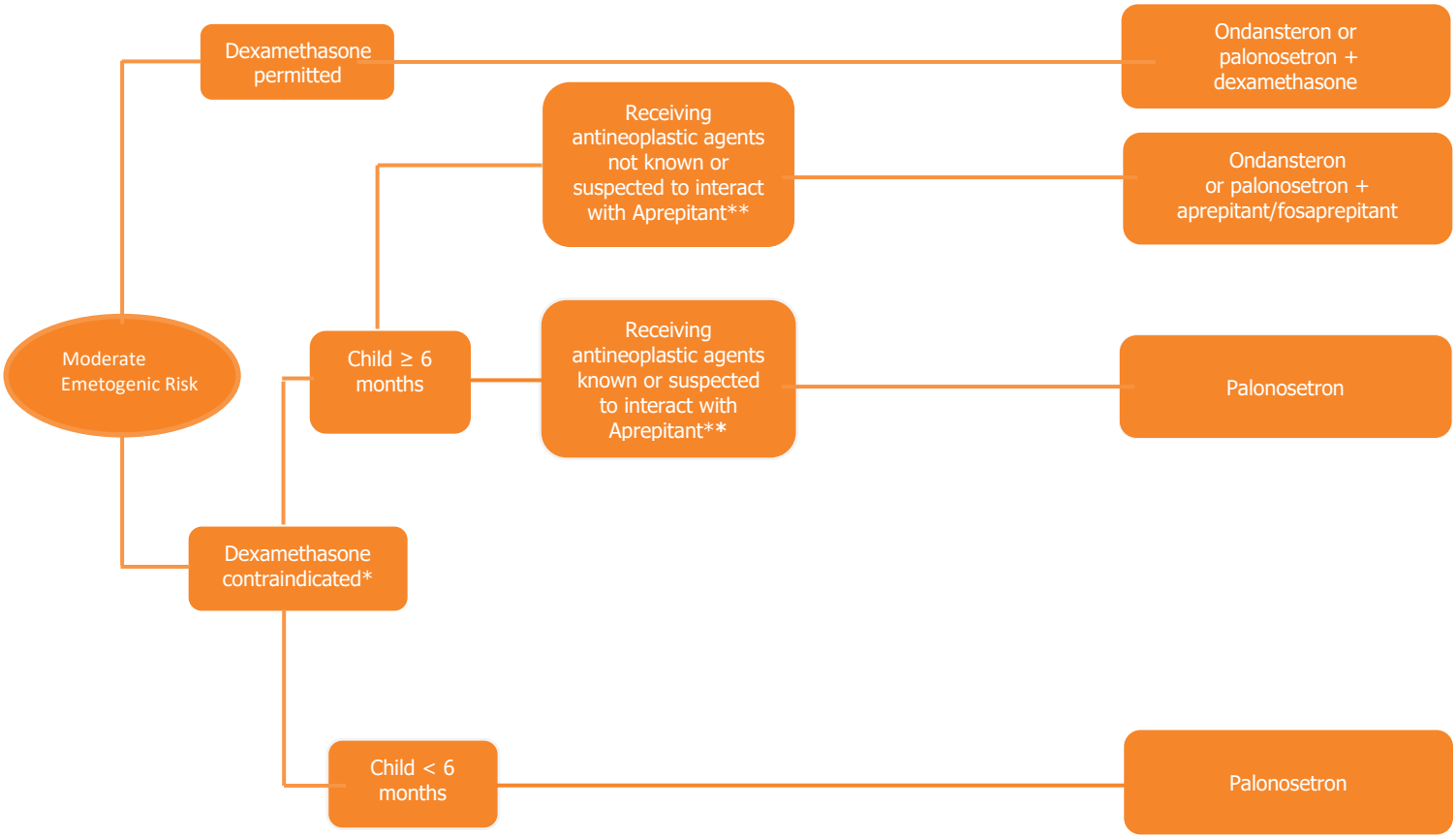
Algorithm 4: APPHON/ROHPPA Prevention of Acute CINV in Pediatric Cancer Patients with LOW Emetogenic Risk (Parenteral Route)

Low Emetogenic Risk	Graniestron Ondansetron	Strong recommendation Low quality evidence

Antineoplastic Agents with LOW Emetic Risk 10% to <30% frequency of emesis in absence of prophylaxis
Single agent antineoplastic therapy
Aldesleukin < 12 Million IU/m²/dose **Blinatumomab** **Bortezomib** **Brentuximab** **Cyclophosphamide ≥ 500 to < 1000 mg/m²/dose** **Docetaxel** **Etoposide** **5-Fluorouracil** **Gemcitabine** **Inotuzumab Ozogamacin** **Liposomal Doxorubicin** **Methotrexate ≤ 250 mg/m²/dose** **Mitoxantrone** **Nelarabine** **Temsirolimus** **Topotecan**
Multiple agent antineoplastic therapy
With the exceptions listed under high emetic risk, emetogenicity is classified based on the most highly emetogenic agent. **Cytarabine 60 mg/m²/dose + mg/m²/dose methotrexate 90 mg/m²/dose**
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**	**Grade**
Granisetron	**Intravenous** 0.04 mg/kg IV daily **Maximum:** 3 mg/dose **Oral** *Round all calculated doses to nearest 1/2 tablet portion (0.5 mg increments)* 0.04 mg/kg PO BID **Maximum:** 2 mg/dose	**IV: Strong recommendation Low quality evidence** **PO: Weak recommendation Low quality evidence**
Ondansetron	**0.1 - 0.2 mg/kg/dose (max 8 mg/dose)** **IV/PO pre-chemotherapy x 1 and up to TID prn**	**Strong recommendation Low quality evidence**

Algorithm 5: APPHON/ROHPPA - Prevention of Acute CINV in Pediatric Cancer Patients with MODERATE Emetogenic Risk (Parenteral Route) Page 1 of 2



***** The use of dexamethasone as an antiemetic is contraindicated in treatment of CNS tumours due to theoretical concern of reduced chemotherapy penetration across the blood brain barrier, hematologic malignancies especially AML due to the increased risk of fungal infection and any study that prohibits the use as an antiemetic. Corticosteroids increase serum glucose monitor for hyperglycemia and limit the use of the steroid to day 1. Steroids also increase the risk of infection and can mask infection by masking fever.

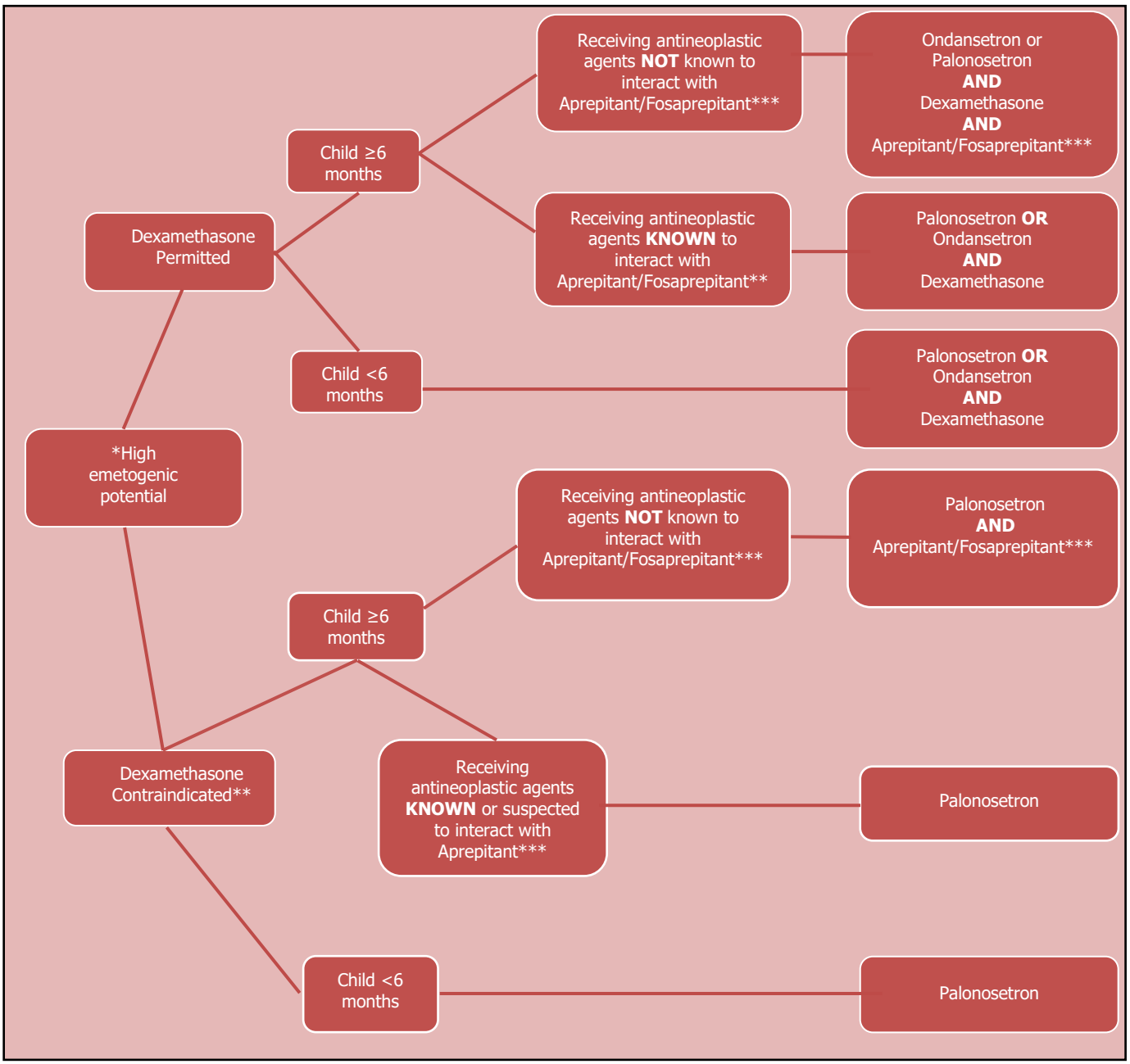
**When prescribing aprepitant always check for interactions with chemotherapy agents; its use with ifosfamide is contraindicated (see drug interaction section of the guideline).

Note: Granisetron can be prescribed in patient's refractory to ondansetron. Consult each study to review any restrictions on the use of antiemetics.

Antineoplastic Agents with MODERATE Emetic Risk 30-90% frequency of emesis in absence of prophylaxis
Single agent antineoplastic therapy
Adesleukin > 12 to 15 million units/m²
Arsenic trioxide
Azacitidine
Bendamustine
Carboplatin < 175 mg/m²/dose
Carmustine ≤250 mg/m²
Clofarabine
Cyclophosphamide > 1000 to < 1500 mg/m²/dose
Cytarabine > 75 mg/m²/dose
Dactinomycin < 0.045 mg/kg/dose
Daunorubicin
Daunorubicin and cytarabine liposomal (CPX-351)
Dinutuximab
Doxorubicin < 30 mg/m²/dose
Gemtuzumab 3-9 mg/m²/dose
Idarubicin
Ifosfamide <2 gram/m²/dose
Interferon apha IV > 15 million U/m²/day
Irinotecan
Methotrexate > 250 mg/m²/dose and < 12 g/m2/dose
Methotrexate IT
Oxaliplatin >75 mg/m²
Multiple agent antineoplastic therapy
With the exceptions listed under high emetic risk, emetogenicity is classified based on the most highly emetogenic agent. Cytarabine IV 100 mg/m²/dose + daunorubicin IV 45 mg/m²/dose + etoposide IV 100 mg/m²/dose + prednisolone PO + thioguanine PO 80 mg/m²/dose Cytarabine IV 60 or 90 mg/m²/dose + methotrexate IV 120 mg/m²/dose Liposomal doxorubicin IV 20-50 mg/m²/dose + topotecan PO 0.6 mg/m²/day
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**	**Grade**
Aprepitant/ Fosaprepitant	**Aprepitant: Greater than or equal to 6 months of age:** **Day 1: 3 mg/kg (maximum 125 mg) PO x 1** **Day 2 & 3: 2 mg/kg (maximum 80 mg) PO once daily (may continue up to day 7 in consultation with pharmacist/oncologist)** **Fosaprepitant (see dosing table pg. 26)**	**Weak recommendation Moderate quality evidence**
Dexamethasone	**≤0.6 m²: 2 mg/dose IV/PO q12 hr** **>0.6m²: 4 mg/dose IV/PO q12hr** **If given concurrently with aprepitant, reduce dexamethasone dose by half**	**Strong recommandation Low quality evidence**
Granisetron	**Intravenous** 0.04 mg/kg IV daily **Maximum:** 3 mg/dose **Oral** *Round all calculated doses to nearest 1/2 tablet portion (0.5 mg increments)* 0.04 mg/kg PO BID **Maximum:** 2 mg/dose	**IV: Strong recommendation Low quality evidence** **PO: Weak recommendation Low quality evidence**
Ondansetron	**(0.1-0.2 mg/kg/dose; maximum 8 mg/dose) IV/PO pre-chemotherapy x 1 and then q8h**	**Strong recommendation Moderate quality evidence**
Palonosetron	**1 month to less than 17 years: 0.02 mg/kg IV once (maximum: 1.5 mg/dose) pre-chemotherapy. May repeat once in 48 hours for multiday chemotherapy.** **Greater than or equal to 17 years: 0.25 mg/dose IV or 0.5 mg/dose PO once pre-chemotherapy. May repeat once in 48 hours for multiday chemotherapy**	**Weak recommendation Moderate quality evidence**

Algorithm 6: APPHON/ROHPPA
Prevention of Acute CINV in Pediatric Cancer Patients with HIGH Emetogenic Risk (Parenteral Route) Page 1 of 2



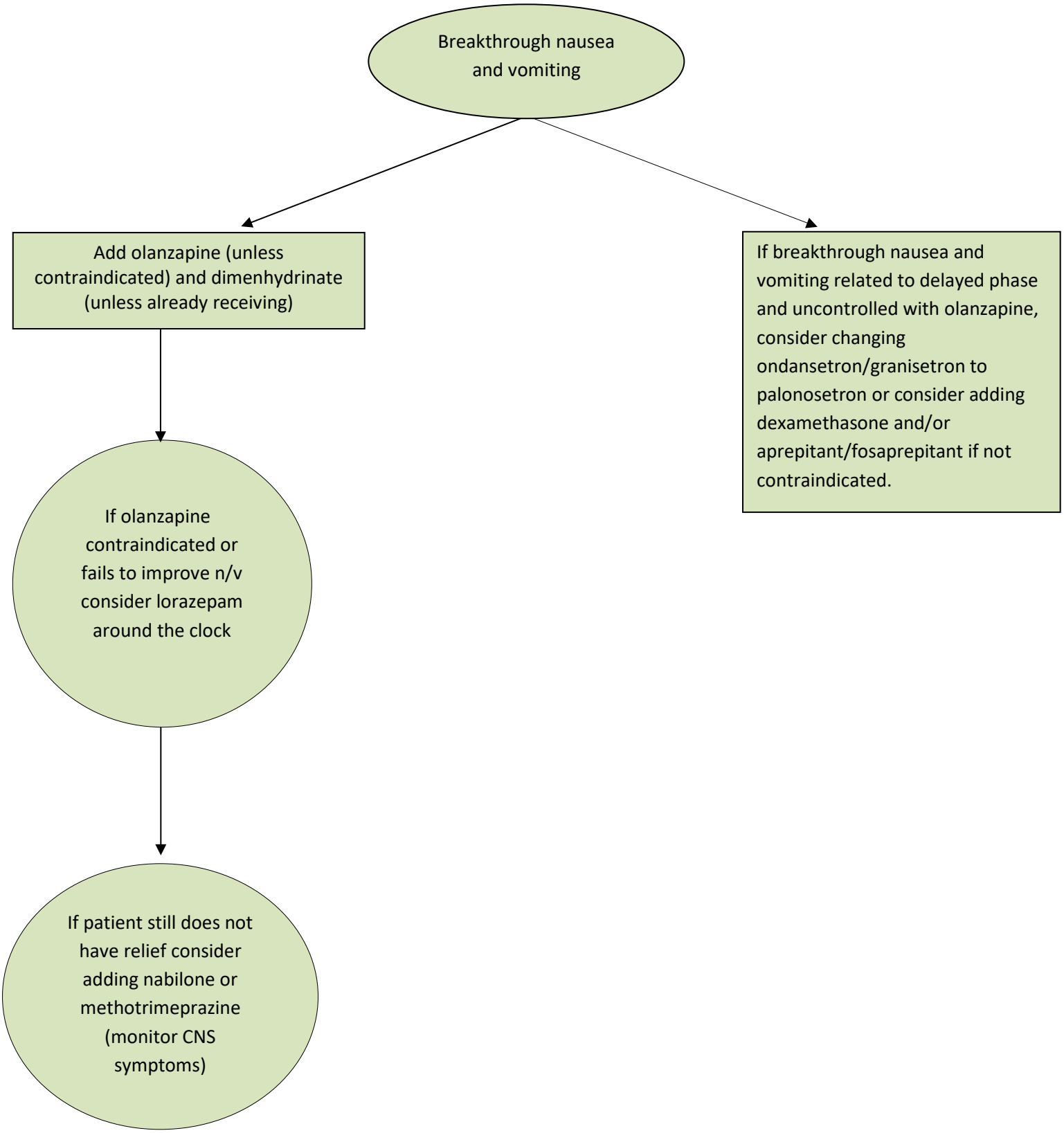
*For patients receiving cisplatin especially multiday chemotherapy or cisplatin or cyclophosphamide + anthracycline or high dose cyclophosphamide/ifosfamide/carboplatin consider prescribing palonosetron in place of ondansetron as palonosetron is more effective in the management of delayed nausea and vomiting.

*The use of dexamethasone as an antiemetic is contraindicated in treatment of CNS tumours due to theoretical concern of reduced chemotherapy penetration across the blood brain barrier, hematologic malignancies especially AML due to the increased risk of fungal infection and any study that prohibits the use as an antiemetic. Corticosteroids increase serum glucose monitor for hyperglycemia and limit the use of the steroid to day 1. Steroids also increase the risk of infection and can mask infection by masking fever.
**When prescribing aprepitant always check for interactions with chemotherapy agents; its use with ifosfamide is contraindicated (see drug interaction section of the guideline). In patients where aprepitant/fosaprepitant is contraindicated may substitute olanzapine + palonosetron + dexamethasone (if not contraindicated)
Note: Granisetron can be prescribed in patient's refractory to ondansetron.
Where aprepitant/fosaprepitant is not permitted consider prescribing palonosetron + dexamethasone + olanzapine (children ≥ 3 years). In children less than 3 years consider palonosetron + dexamethasone.
Consult each study to review any restrictions on the use of antiemetics.

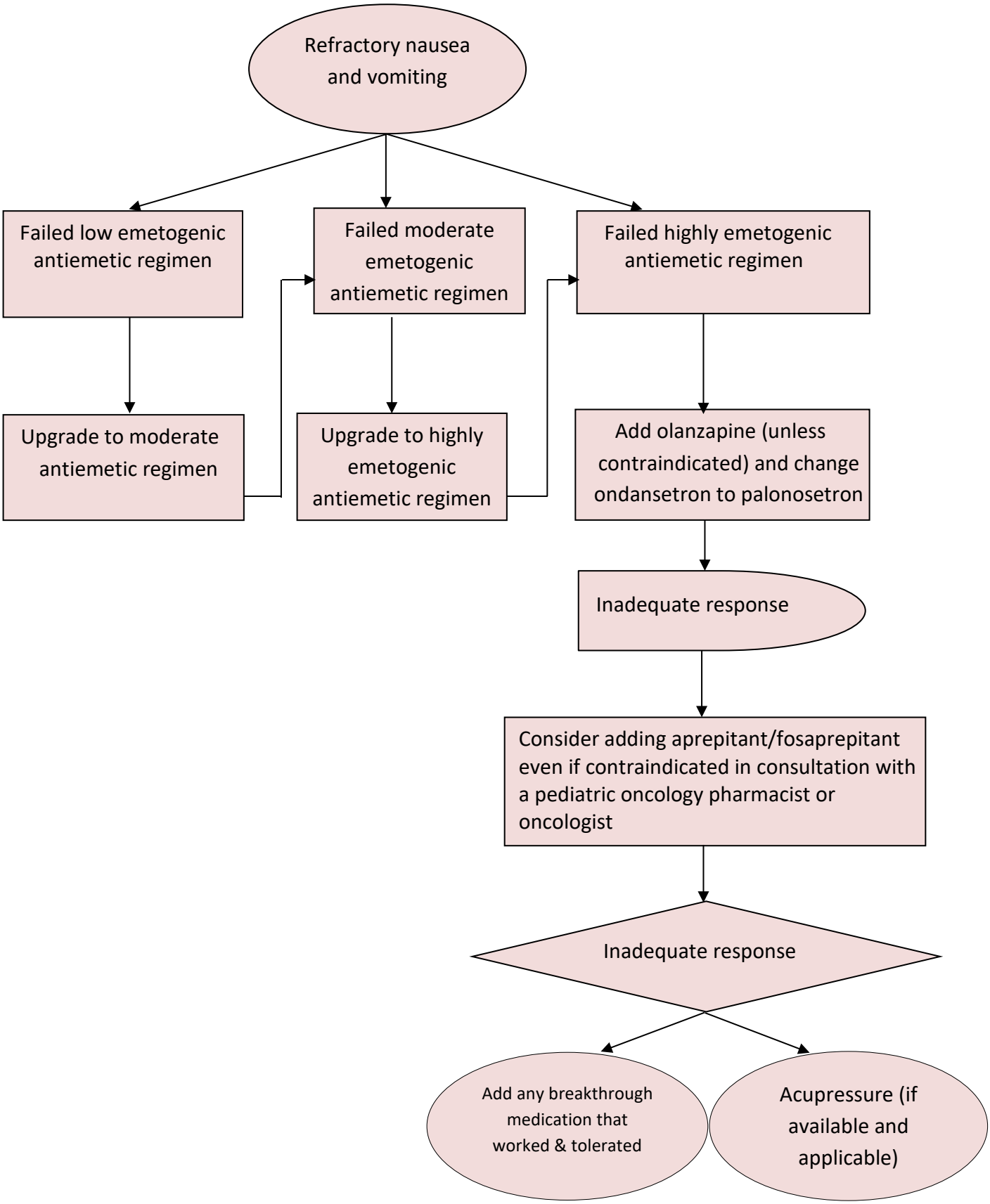
Antineoplastic Agents with HIGH Emetic Risk >90% frequency of emesis in absence of prophylaxis
Single agent antineoplastic therapy
Asparaginase (Erwinia) IV **Carboplatin ≥ 175 mg/m²/dose** **Carmustine >250 mg/m²/dose** **Cisplatin** **Cyclophosphamide ≥ 1,500 mg/m²/dose** **Cytarabine ≥ 3 g/m²/dose** **Dactinomycin ≥ 0.045mg/kg/dose** **Doxorubicin ≥ 30mg/m²/dose** **Ifosfamide ≥ 2gram/m²/dose** **Methotrexate ≥12 g/m²**
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 ≥ 600 mg/m² /dose + dactinomycin ≥ 1 mg/m² /dose** **Cyclophosphamide ≥ 400 mg/m² /dose + doxorubicin ≥ 40 mg/m² /dose** **Cytarabine ≥ 90 mg/m² /dose + methotrexate ≥ 150 mg/m² /dose** **Dacarbazine ≥ 250 mg/m² /dose + doxorubicin ≥ 60 mg/m² /dose** **Dactinomycin ≥ 0.9 mg/m² /dose + ifosfamide ≥ 3 g/m² /dose** **Doxorubicin + ifosfamide** **Doxorubicin + methotrexate ≥ 5 g/m²** **Etoposide ≥ 60 mg/m² /dose + ifosfamide ≥ 1.2 g/m² /dose** **Anthracycline + cyclophosphamide** **Cyclophosphamide + etoposide** **Cytarabine 150-200 mg/m²/dose + daunorubicin** **Cytarabine 300 mg/m²/dose + etoposide**
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/ Fosaprepitant**	**Greater than or equal to 6 months:** **Pre-Chemotherapy** **Day 1: 3 mg/kg (maximum 125 mg) PO x 1** **Day 2 & 3: 2 mg/kg (maximum 80 mg) PO** **Fosaprepitant (see dosing table pg 26) once daily**
Dexamethasone	**6 mg/m²/dose IV/PO once daily pre-chemotherapy may increase to q 12 h (maximum 20 mg/day)** **If given concurrently with aprepitant/fosaprepitant, reduce dexamethasone dose by half**
Granisetron	**Intravenous** 0.04 mg/kg IV daily **Maximum:** 3 mg/dose **Oral** *Round all calculated doses to nearest 1/2 tablet portion (0.5 mg increments)* 0.04 mg/kg PO BID **Maximum:** 2 mg/dose
Ondansetron	**0.1-0.2 mg/kg/dose (maximum 8 mg/dose) IV/PO pre-therapy x 1 and then every 8 hours**
Palonosetron	**1 month to less than 17 years: 0.02 mg/kg IV once (maximum: 1.5 mg/dose) pre-chemotherapy. May repeat once in 48 hours for multiday chemotherapy.** **Greater than or equal to 17 years: 0.25 mg/dose IV or 0.5 mg/dose PO once pre-chemotherapy. May repeat once in 48 hours for multiday chemotherapy.**

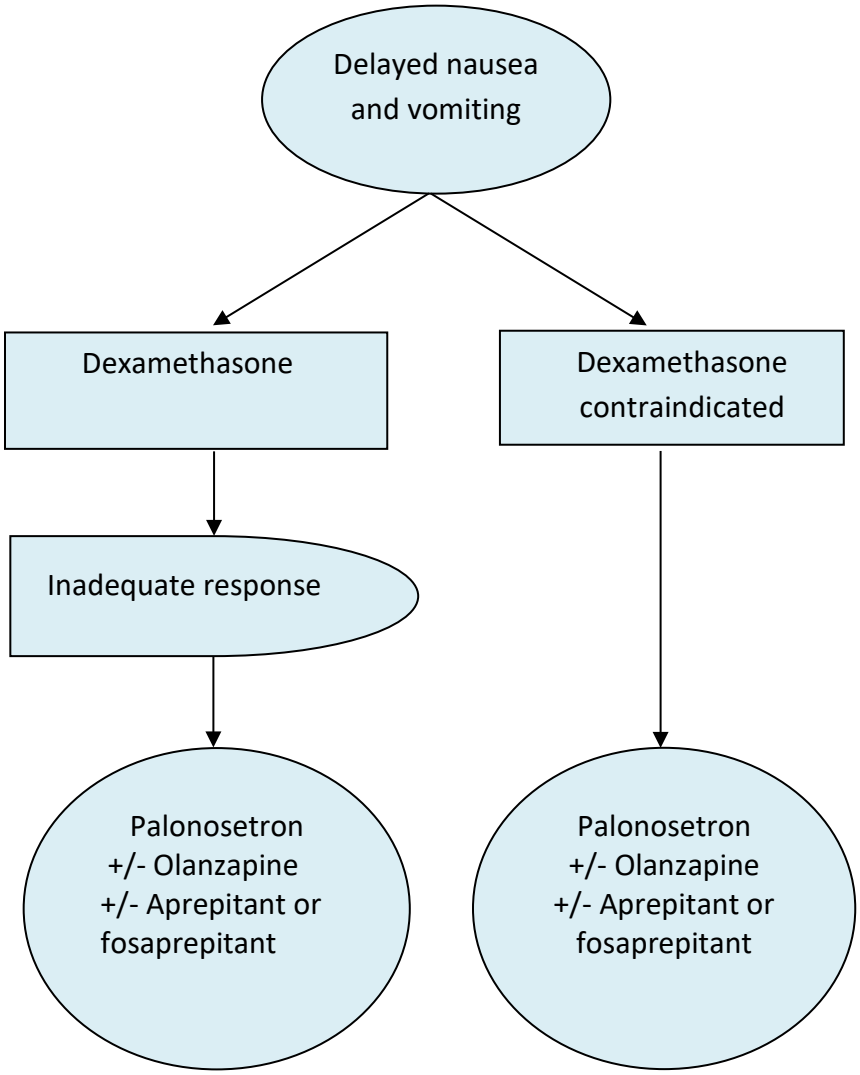
Algorithm 7: Management of Breakthrough Nausea and Vomiting During a Cycle of Chemotherapy



Algorithm 8: Management of Refractory Nausea and Vomiting



Algorithm 9: Management of Delayed Nausea and Vomiting



Algorithm 10: Management of Anticipatory Nausea and Vomiting

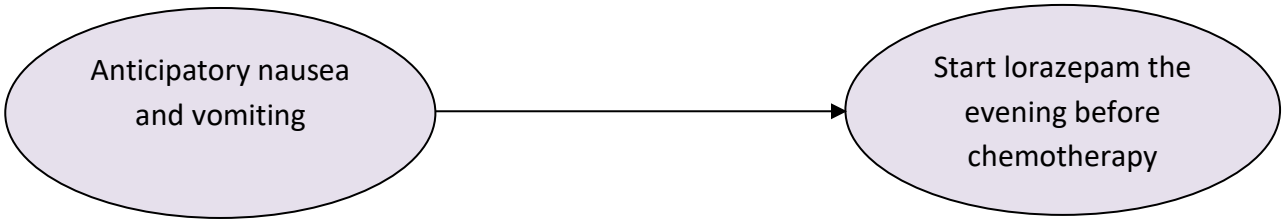


Table 1: Antiemetics, dosing and level of evidence for use

Antiemetic	Indication	Dosing	Strength of recommendation and grade of evidence
Aprepitant	Acute and delayed	Greater than or equal to 6 months: Day 1: 3 mg/kg (maximum 125 mg) PO x 1 Day 2 & 3: 2 mg/kg (maximum 80 mg) PO once daily May be extended up to 7 days (limited data)	Weak recommendation Moderate quality of evidence
Fosaprepitant		Infants ≥6 months weighing ≥6 kg and Children <2 years: Single day: 5 mg/kg IV (maximum 150 mg/dose) 3-day: 3 mg/kg IV (maximum 115 mg/dose) on day 1 followed by aprepitant on day 2 and 3. 2-12 years: Single day: 4 mg/kg IV (maximum 150 mg/dose) 3-day: 3 mg/kg IV (maximum 115 mg/dose) on day 1 followed by aprepitant on day 2 and 3. Greater than or equal to 12 years: Single day: 150 mg IV x 1 3-day: 115 mg IV on day 1 followed by aprepitant on day 2 and 3.	Weak recommendation Moderate quality of evidence
Dexamethasone	Acute and delayed	Moderately emetogenic regimen: ≤0.6 m^2: 2 mg/dose IV/PO q12 hr >0.6m^2: 4 mg/dose IV/PO q12hr. If given concurrently with aprepitant/fosaprepitant, reduce dexamethasone dose by half Highly emetogenic regimen: 6 mg/m^2/dose IV/PO once daily may increase to q12 h (maximum 20 mg/day) If given concurrently with aprepitant/fosaprepitant, reduce dexamethasone dose by half	Highly emetogenic: Weak recommendation Low quality of evidence Moderately emetogenic: Strong recommendation Low quality of evidence
Dimenhydrinate	Breakthrough	Children ≥ 1 year of age: 1 mg/kg (maximum 50 mg/dose) IV/PO q4h as needed for breakthrough nausea and vomiting upfront in all patients. Children less than 1 year should start with 0.5 mg/kg and titrate to effect to minimize paradoxical reactions	Weak recommendation Low quality of evidence

Granisetron	Acute (use in patient refractory to ondansetron)	**Intravenous** 0.04 mg/kg IV daily **Maximum:** 3 mg/dose **Oral** *Round all calculated doses to nearest 1/2 tablet portion (0.5 mg increments)* 0.04 mg/kg PO BID **Maximum:** 2 mg/dose	Strong recommendation Moderate quality of evidence
Lorazepam	Anticipatory and breakthrough	5-10 years: 0.5 mg/dose Greater than 10 years: 1 mg/dose PO/SL/IV first dose night before chemotherapy and repeat a dose morning before chemotherapy and then q8h as needed	Strong recommendation Moderate quality of evidence
Methotrimeprazine	Breakthrough	Infants, Children and Adolescents (oral dosing): 0.25 mg/kg/24hrs in 2 to 3 divided doses; may titrate to effect (maximum dose for children ≤12 years: 25 mg/day) Children and Adolescents (IV dosing): (IWK oncology/palliative care service recommendation): 0.0625 mg/kg/24hr (maximum 2 mg/dose) IV over 30 minutes-1 hour if given through a central line q8h –q24hr (monitor for hypotension)	Weak recommendation Low quality of evidence
Nabilone	Breakthrough	≥ 4 years <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 Note: May need to titrate to effect	Weak recommendation Low quality of evidence
Olanzapine	Breakthrough and delayed	Greater than 3 years: 0.1 mg/kg/dose (maximum 10 mg/dose) once or twice daily (round to nearest whole of portion of tablet strength) Caution in children with psychiatric conditions.	Weak recommendation Low quality of evidence
Ondansetron	Acute	0.1- 0.2 mg/kg/dose (max 8 mg/dose) IV/PO pre chemotherapy x 1 and up to TID prn	Strong recommendation Moderate quality of evidence
Palonosetron	Acute and delayed/refractory	1 month to less than 17 years: 0.02 mg/kg IV once (maximum: 1.5 mg/dose) pre-chemotherapy. May repeat once in 48 hours for multiday chemotherapy. Greater than or equal to 17 years: 0.25 mg/dose IV or 0.5 mg/dose PO once pre-chemotherapy. May repeat once in 48 hours for multiday chemotherapy NOTE: higher dosing is required in children as the 3-fold higher systemic exposure produced the same response as seen in adults.	Weak recommendation Moderate quality of evidence

DEVELOPMENT AND REVIEW:

Prepared by: Tamara MacDonald PharmD
Expert Review: Included pediatric oncologists (IWK and Janeway) and pharmacists, pediatricians and nurses.
Stakeholder Review: APPHON/ROHPPA Multidisciplinary Health Care Providers (For more information please contact APPHON/ROHPPA)

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APPENDIX 1:

Differences in the APPHON recommendations and the POGO Guideline for the Prevention of Acute Nausea and Vomiting due to Antineoplastic Medication in Pediatric Cancer Patients

	POGO	APPHON	COMMENTS
Dexamethasone	Highly emetogenic regimen: 6 mg/m^2 /dose IV/PO q6h If given concurrently with aprepitant, reduce dexamethasone dose by half. Weak recommendation Low quality evidence	Highly emetogenic regimen: 6 mg/m^2/dose IV/PO once daily may increase to q 12 h (maximum 20 mg/day) If given concurrently with aprepitant, reduce dexamethasone dose by half	Adult guidelines (NCCN, ASCO) recommend the use of dexamethasone as an antiemetic with a daily maximum of 20 mg. Usually given as a 12 mg in the morning and followed by 8mg in the evening for highly emetogenic chemotherapy regimens. Giving higher than adult recommended dose and possibly as high as 50 mg of dexamethasone per day was not felt to be best practice as dexamethasone has many adverse effects and anecdotally the 20 mg maximum has been sufficient with little evidence to suggest that higher doses provide better antiemetic control.