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

Tamara MacDonald PharmD

tamara.macdonald@iwk.nshealth.ca

Conflicts of Interest

- none

Guideline working group

- Multidisciplinary
- Interprovincial

Evidence documents for the guideline:

Pediatric Oncology Group of Ontario provided pediatric evidence:

- **Guideline for the prevention of acute chemotherapy-induced nausea and vomiting in pediatric cancer patients (February 2017)**
- **Guideline for the prevention and treatment of anticipatory nausea and vomiting due to chemotherapy in pediatric cancer patients (March 2021)**
- **Classification of the acute emeticity of chemotherapy in pediatric patients: A clinical practice guideline (January 2019).**

- Where pediatric evidence was not available the following were used to make recommendations regarding emeticity of commonly used chemotherapy agents in pediatrics:
  - **National Comprehensive Cancer Network NCCN Antiemesis guideline (2020)**
  - **Multinational Association of Supportive Care in Cancer (MASCC/ESMO) antiemetic guideline updated 2019**
  - **American Society of Clinical Oncology ASCO antiemetics guideline (Hesketh et al; 2020)**
- Where discrepancies occurred between these documents with respect to the level of emeticity of the agents, the higher emetic potential was used.

Why we didn’t adopt the Pediatric Oncology Group of Ontario (POGO) guideline

- POGO does not recommend a maximum dose for dexamethasone due to lack of studies in pediatrics.
- APPHON extrapolated the adult maximum dose of 20 mg/day as it is felt that nausea and vomiting is controlled at this dose without incurring unnecessary toxicity.
- POGO only reports on chemotherapy agents that have supporting data in pediatrics.
- APPHON includes all commonly administered chemotherapy agents based on extrapolation from adult data from international groups including the national comprehensive cancer network (NCCN) and the multinational association of supportive care in cancer (MASCC). Note: Oral chemotherapy agents are understudied and as such the management and emetic potential of these agents is based on best practices.

Purpose

- 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.
- 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.

Target audience

- The target audience of this guideline is the healthcare providers involved in the care of children with cancer in the Atlantic Provinces.

Highlights of what has changed from 2018 version:

- Update and addition of chemotherapy agents
- Some evidence informed changes to the emetic potential of agents
- More specific information on how to treat refractory/breakthrough and delayed CINV
- Separation of oral and parenteral chemotherapy
- Information on drug interactions with aprepitant/fosaprepitant
- Antiemetic dosing updates
- Removal of scopolamine patch as has been discontinued

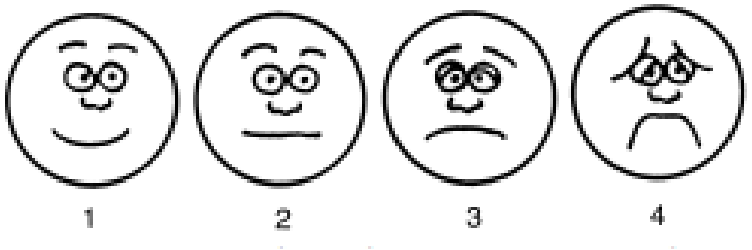
Types of chemotherapy induced nausea and vomiting (which includes retching) will be discussed in this guideline:

- 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 emetic potential:

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

Nausea and vomiting assessment:



- The number and volume of emesis should be recorded daily.
- Nausea is more difficult to assess.
- Institutional practices of assessment and documentation of nausea in children should be followed.
- PeNAT (pediatric nausea assessment tool) 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 to determine the language that each family uses to describe nausea and vomiting.

PeNAT cont'd

Excerpt of questions from the PeNAT questionnaire given to families.

- 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?

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

Non-pharmacologic management of chemotherapy induced nausea and vomiting

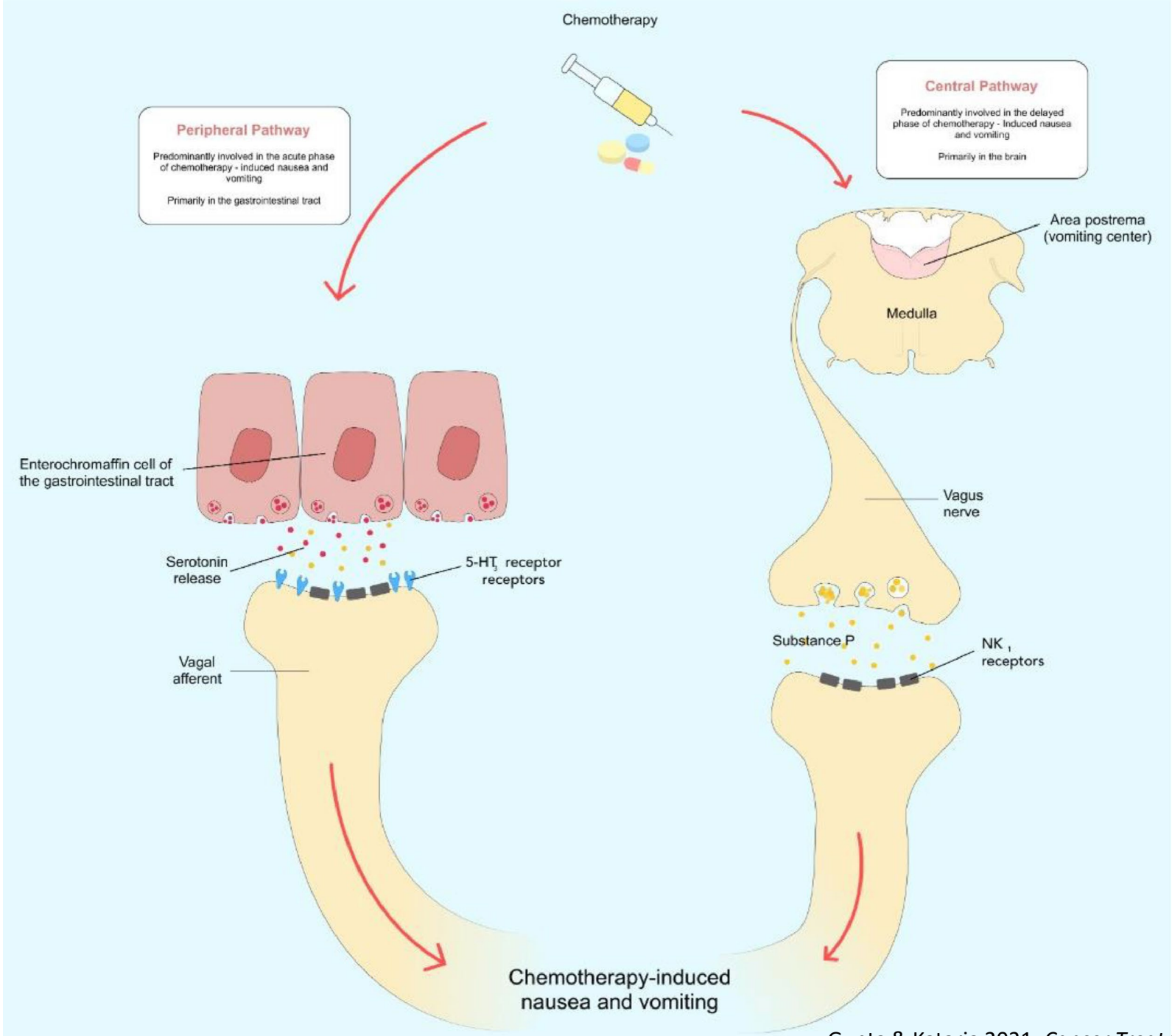
- Some suggested non-pharmacological interventions may include *music therapy, cognitive distraction, guided imagery, massage, acupressure and dietary concerns*. These non-pharmacologic interventions are beyond the scope of this guideline and will not be discussed except for dietary concerns.

Pharmacologic management of chemotherapy induced nausea and vomiting

- Guiding principles of nausea and vomiting prevention and management:
  - 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.
  - 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.
  - The emetic potential of the chemotherapy cycle dictates the approach to management of CINV for each chemotherapy cycle is based on the agent with the highest emetic potential.

Pathophysiology of CINV:

- Two primary mechanisms have been suggested in the pathophysiology of the emetic response.
  - One is through a central pathway that includes the *chemoreceptor trigger zone*, an area located outside of the blood-brain barrier in the medulla oblongata responsible for delayed emesis.
  - The other is through a peripheral pathway involving the vagal afferent nerves in the gastrointestinal tract responsible for acute emesis.
- Various neurotransmitter receptors including dopamine, 5-hydroxytryptamine type 3 (5-HT_3, serotonin), and neurokinin-1 (NK-1) are activated by chemotherapy, causing an emetic response.



Gupta & Kataria 2021, *Cancer Treatment and Research Communications*

Chemotherapy and emetic response:

Activation of the peripheral pathway is primarily associated with acute CINV.

- Chemotherapeutic drugs can activate neurotransmitter receptors in the area postrema in the medulla of the brain or stimulate vagal afferents near the enterochromaffin cells in the intestine.
- The peripheral pathway is activated within 24 h after initiation of chemotherapy by the oxidative action of free radicals generated by chemotherapeutic agents, which stimulate enterochromaffin cells in the gastrointestinal tract to release serotonin.
- Serotonin subsequently stimulates abdominal afferent vagal fibers as part of the peripheral emesis pathway and activates the emetic response via the vomiting center.

Activation of the central pathway is associated with delayed CINV:

- Chemotherapy drugs (e.g., cisplatin, carboplatin, anthracycline, cyclophosphamide and ifosfamide) can also elicit the release of substance P in both the central and peripheral nervous systems, resulting in NK1-mediated vomiting.
- The results of clinical trials for 5HT3 and NK1 receptor antagonists further support a principal role for central NK1 activation in delayed CINV.
- Dopamine receptors are present in the CTZ and VC and as such dopamine antagonist have some protection against delayed n/v

Nausea pathway not well understood:

- A majority of findings indicate that centrally expressed NK1 receptors are responsible for nausea as the result of chemotherapy-induced substance P release.

Other factors to consider before changing an antiemetic regimen:

- Before considering any change in the antiemetic regimen, it is important to exclude other disease- and medication-related causes for emesis. Examples include the following:
  - The use of opiate analgesics
  - Certain antibiotics
  - Central nervous system metastases
  - Gastrointestinal obstruction
  - Hypercalcemia
  - Abdominopelvic radiation therapy
- Ensure the antiemetics prescribed are being administered.

Antiemetic classes:

Acute phase active agents:

- Serotonin (5-HT3) antagonists: Ondansetron, granisetron
- Histamine 1 antagonists: Dimenhydrinate.
- Dopamine antagonists: Metoclopramide.
- Muscarinic antagonists: Scopolamine patch.
- Cannabinoids: Nabilone.
- Benzodiazepines: Lorazepam.
- Typical antipsychotics: Methotrimeprazine

Delayed phase active agents:

- NK-1 receptor antagonists: Aprepitant and fosaprepitant.

Both acute and delayed phase agents:

- Corticosteroids: Dexamethasone.
- Atypical antipsychotics: Olanzapine (dopamine and serotonin antagonist)
- Serotonin (5-HT3) antagonists: Palonosetron

Mechanism of action of first-generation serotonin (5-HT3) antagonists in CINV:

Two first generation 5-HT3 receptor antagonists in use today:

- Ondansetron:
  - A selective 5-HT3 receptor antagonist with weak affinity for other 5-HT receptors and dopamine receptors.
  - Half-life 4 hours.
  - Significant QTc prolongation with doses greater than 16 mg, IV route and rapid administration
  - Acute n/v
- Granisetron:
  - A selective 5-HT3 receptor antagonist.
  - Half-life 9 hours
  - May be prescribed in patients who fail ondansetron due to cross resistance
  - Acute n/v

AEs: Headache and constipation and QTc prolongation, serotonin syndrome can occur with any 5-HT3 antagonist - confusion, agitation, restlessness, muscle twitching or stiffness, fever, sweating, fluctuations in heart rate and blood pressure, as well as nausea and/or vomiting, loss of consciousness, and coma (avoid with other agents that can increase serotonin levels)

Mechanism of action of second generation 5-HT3 antagonists in CINV:

Palonosetron:

- Binds to 5-HT3 receptors more avidly than the 1st generation 5-HT3 antagonists and it exhibits allosteric binding (strong) in contrast to the pure competitive binding seen with first-generation agents.
- It has a different chemical structure that allows for a longer half-life of 42 hours.
- It causes receptor internalization which result in additional prolongation of duration (the receptors stop working)
- The superior receptor binding is thought to be the reason for the increased efficacy of palonosetron over the first generation agents and not its longer half-life.
- Receptor cross-talk is proposed to occur with palonosetron so both the NK1 receptor and the 5-HT3 receptor are blocked which is the proposed mechanism of the efficacy of this drug in controlling delayed nausea and vomiting.
- Oral bioavailabilty is 97%
- Little effect on QTc

Mechanism of action of NK-1 receptor antagonists in CINV:

Aprepitant:

- Blocks Nk-1 receptors that are activated by substance P in the brain and gut.
- It is very effective in combination with a 5-HT3 inhibitor and dexamethasone in the management of acute and delayed onset vomiting in highly emetic protocols.
- It should be included with chemotherapy agents that can cause delayed nausea and vomiting as it blocks substance P which is thought to cause delayed n/v.
- Cisplatin causing CINV in a biphasic pattern with the acute phase lasting up the 24 hours with a nadir and then the delayed phase peaks at 48hrs and can continue for several days. Aprepitant should be used along with palonosetron and dexamethasone for optimal CINV control.

Fosaprepitant:

- Intravenous prodrug of aprepitant.
- Studies show one day fosapretant (day 1) equivalent to 3 day aprepitantz.
- Bioequivalent to aprepitant.
- 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.

AEs: fatigue, asthenia, hiccups.

Mechanism of corticosteroids in the control of CINV:

- Dexamethasone mechanism of action is not clear since the protective effect occurs much sooner than conventional corticosteroid mechanism would allow.
- Dexamethasone prolonged half-life appears to provide some relief for delayed nausea and vomiting.
- Onset of action is rapid.
- Multiple studies have shown benefit in delayed, breakthrough and refractory n/v.
- The Italian Group of Antiemetic Research has defined the optimal dosing of dexamethasone for CINV in adults receiving highly emetogenic chemotherapy at 20 mg/day.
- The optimal dose in moderately emetogenic chemotherapy is proposed at 8 mg/day greater than 0.6 m^2 and 4 mg/day less than 0.6 m^2.
- AEs: insomnia, hyperglycemia, heartburn and leukocytosis.

Mechanism of action of Cannabinoids in CINV:

- Nabilone is a cannabinoid that is currently used for CINV in patients who have not adequately responded to conventional antiemetics.
- Cannabinoids are thought to prevent nausea and vomiting by stimulating cannabinoid receptor CB_1 in the CNS and possibly CB_2 receptors as well.
- Cannabinoids have been shown to be as effective as or slightly more effective than dopamine receptor antagonists.
- Only 1 trial has directly compared a cannabinoid with standard treatment and found little benefit of cannabinoid over conventional antiemetics.
- Currently cannabinoids have limited use in the preventive setting.
- Can be used in refractory or breakthrough n/v.
- AEs: vertigo, euphoria, and somnolence are adverse effects that limit the use of cannabinoids.

Mechanism of action of benzodiazepines in CINV:

- Benzodiazepines are anxiolytics.
- These agents are appropriate adjunct therapies to decrease treatment-related anxiety, and they are the preferred agents to treat and prevent anticipatory nausea and vomiting.
- Lorazepam and alprazolam are the primary agents used in this class, with sedation being the most common adverse effect, based on our clinical practice experience.

Mechanism of action of antipsychotics in CINV:

Second generation (atypical) antipsychotics: Olanzapine

- Have antagonist activity at histamine receptors, muscarinic receptors, and multiple dopamine ($D_{1–4}$) and serotonin receptors (5-HT 2,3 and 6).
- Several trials have shown that olanzapine safely and effectively prevents acute, delayed, and refractory CINV when combined with other antiemetics in patients receiving moderately and highly emetogenic chemotherapy possible due to its effect on multiple receptors in the central pathway.

First generation (typical) antipsychotics: Methotrimeprazine

- Have antagonist activity at dopamine D2 and weakly at serotonin receptors.

AEs: sedation, weight gain, orthostatic hypotension, hyperglycemia.

Mechanism of emesis control by histamine antagonists (H1) in CINV:

- Dimenhydrinate competes with histamine for H_1-receptor sites on effector cells in the gastrointestinal tract, blood vessels, and respiratory tract; blocks chemoreceptor trigger zone, diminishes vestibular stimulation, and depresses labyrinthine function through its central anticholinergic activity.
- Efficacy in controlling breakthrough nausea.
- AEs: Sedating.

Mechanism of dopamine antagonists in CINV:

- Metoclopramide antagonizes dopamine, but at high doses it also has activity against the 5-HT_3 receptor.
- Dopamine receptor antagonists are mostly used in the management of breakthrough or refractory emesis since the advent of more potent antiemetics.
- The dopamine antagonists are divided into phenothiazines (eg, prochlorperazine), butyrophenones (eg, haloperidol, droperidol), and substituted benzamides (eg, metoclopramide).
- AEs: extrapyramidal symptoms, dystonia, and drowsiness, make them more suitable for breakthrough nausea rather than for primary prophylaxis.

Mechanism of action of anticholinergic agents in CINV:

- Anticholinergic agents (M1-muscarinic receptor antagonists) : ex. scopoloamine patch (Transderm V), blocks the action of acetylcholine at parasympathetic sites in smooth muscle, secretory glands and the CNS; increases cardiac output, dries secretions, antagonizes histamine and serotonin.
- Reduces secretions.
- Prescribed in refractory nausea and vomiting.
- DISCONTINUED.

Receptor specific antiemetics:

	serotonin	CB-1/CB-2	histamine	dopamine	NK-1
	Acute phase receptors				Delayed phase receptor
ondansetron/ granisetron	●				
palonosetron	●				•
Aprepitant/ fosaprepitant					●
olanzapine	●		●	●	
methotrimeprazine	•			●	
metoclopramide	•			●	
dimenhydrinate			●		
nabilone		●			

Monitoring for QT-c prolongation

- ECG not required unless previous QTc prolongation or significant hypokalemia or hypomagnesemia, heart failure, and bradyarrhythmias, and in patients taking other medications that increase the risk of QTc prolongation.
- Antiemetics associated with QTc prolongation:
  - First generation serotonin antagonist: More severe when administered IV and at higher doses.
  - Second generation serotonin antagonist: Palonosetron has insignificant QTc prolongation.
  - Antipsychotics:
    - Second generation antipsychotic olanzapine mild QTc prolongation.
    - First generation methotrimeprazine moderate QTc prolongation.

Contraindications/Cautions to specific antiemetics:

- Dexamethasone:
  - AML – increased infectious complications
  - Central nervous system tumors – theoretical decrease in BBB penetration
  - Unhealed wounds
  - Study prohibits use
- Aprepitant/fosaprepitant:
  - Multiple drug interactions
  - Age less than 6 months
- Prolong QT (requires ECG monitoring):
  - receiving multiple drugs known to prolong QT
  - Significant clinical history of QT prolongation
- Antipsychotics:
  - Clinical history of psychiatric disorder
  - Age less than 3 years
- Sedation:
  - Caution in using multiple sedating agents together e.g., lorazepam, dimenhydrinate, methotrimeprazine.

Drug interactions with aprepitant/fosaprepitant CYP3A4 inhibitors/ inducers:

	Contraindicated	Caution
ifosfamide	●	
cyclophosphamide		●
Vincristine/vinblastine/vinorelbine		●
Doxorubicin/daunorubicin		●
etoposide		●
Imatinib/dasatinib		●
irinotecan		●
lorazepam		●
Fluconazole/voriconazole		● (reduce the dose of aprepitant/fosaprepitant)
Dexamethasone		● (reduce dexamethasone dose by half)

Mechanisms of interaction with all drugs that are a CYP3A4 substrates:

1) Increase the serum concentration of the substrate – increases toxicity of the chemotherapy agent (most common)
2) Increase the clearance of the substrate – decreases efficacy of the chemotherapy agent (usually happens in conjunction with #1)
3) Slow conversion of prodrug to active form – alters the time to effect of the chemotherapy agent

Young children and those with inflammatory conditions such as cancer may have more clinically significant interactions due to the reduce prevalence (age) and function of CYP3A4 and hepatic drug transporters.

These interactions are dose dependent and as such are less significant with one day dosing.

Fosaprepitant is a weak inhibitor of CYP3A4 so has less potential for resulting in clinically significant interactions.

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 — **Granisetron** / **Ondansetron** — **Strong recommendation, Low quality evidence**

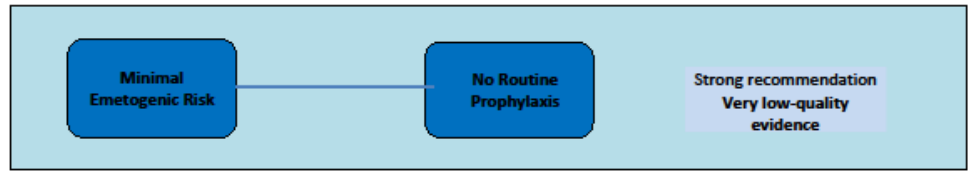
Antineoplastic Agents with MINIMAL to Low Emetic Risk <10% frequency of emesis in absence of prophylaxis		Antiemetic Dosage Recommendations for Children receiving Minimal to LOW Emetic Risk Antineoplastic Therapy		
Single agent antineoplastic therapy		**Drug**	**Dose**	**Grade**
Dasatinib Decitabine 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

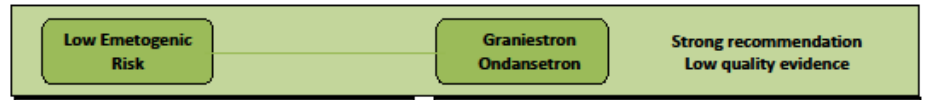
Antineoplastic Agents with MODERATE TO HIGH Emetic Risk ≥ 30% frequency of emesis in absence of prophylaxis	Antiemetic Dosage Recommendations for Children receiving MODERATE to HIGH Emetic Risk Antineoplastic Therapy		
Single agent antineoplastic therapy	**Drug**	**Dose**	**Grade**
Crizotinib Cyclophosphamide 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.

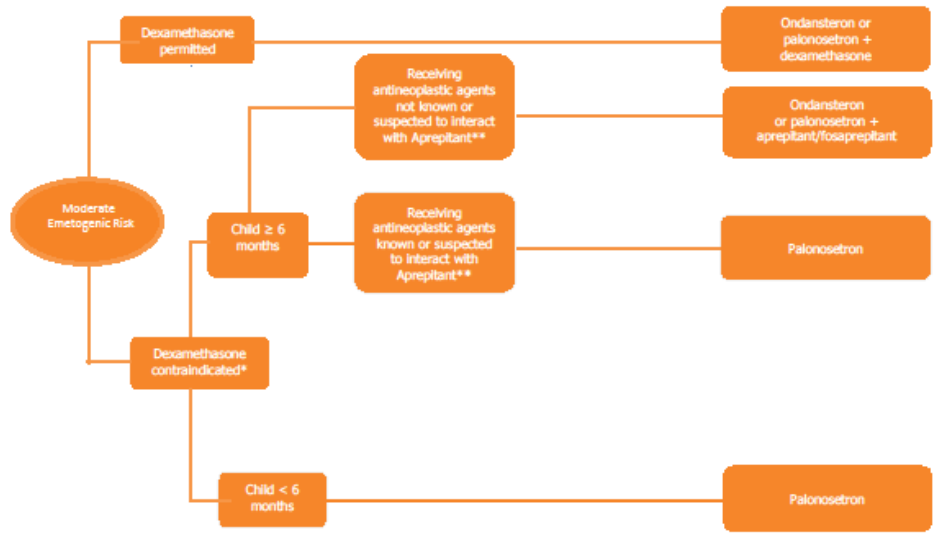
Algorithm 4: APPHON/ROHPPA Prevention of Acute CINV in Pediatric Cancer Patients with LOW Emetogenic Risk (Parenteral Route)



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



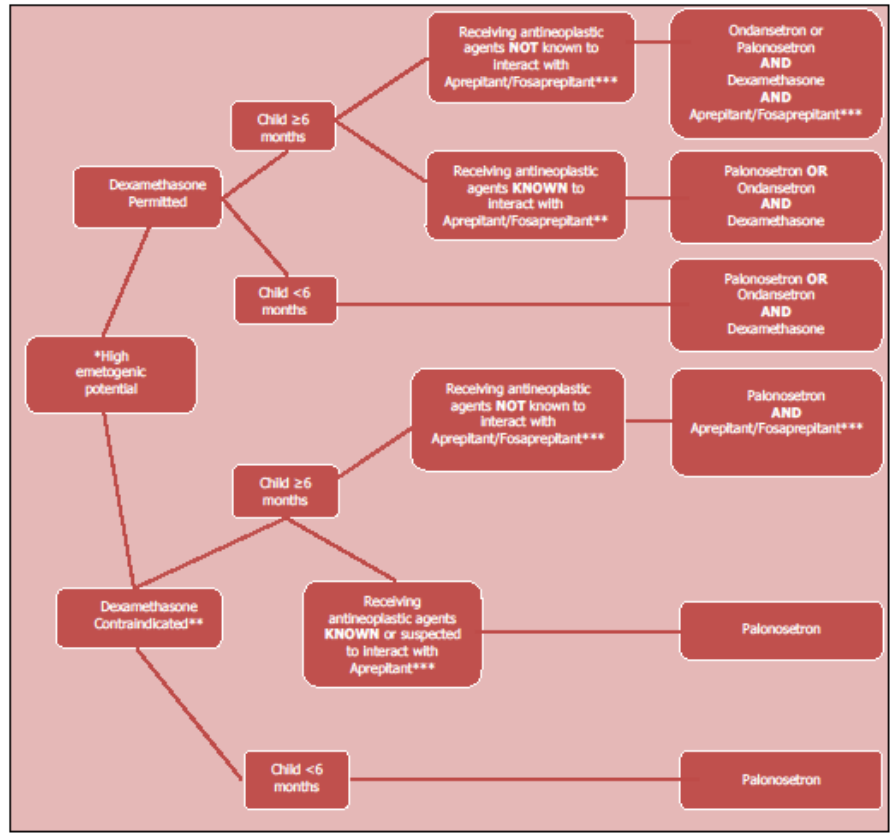
* The use of dexamethasone as an antiemetic is contraindicated in treatment of CNS tumours due to theoretical concern of reduced chemotherapy penetration across the blood brain barrier, hematologic malignancies especially AML due to the increased risk of fungal infection and any study that prohibits 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.

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)



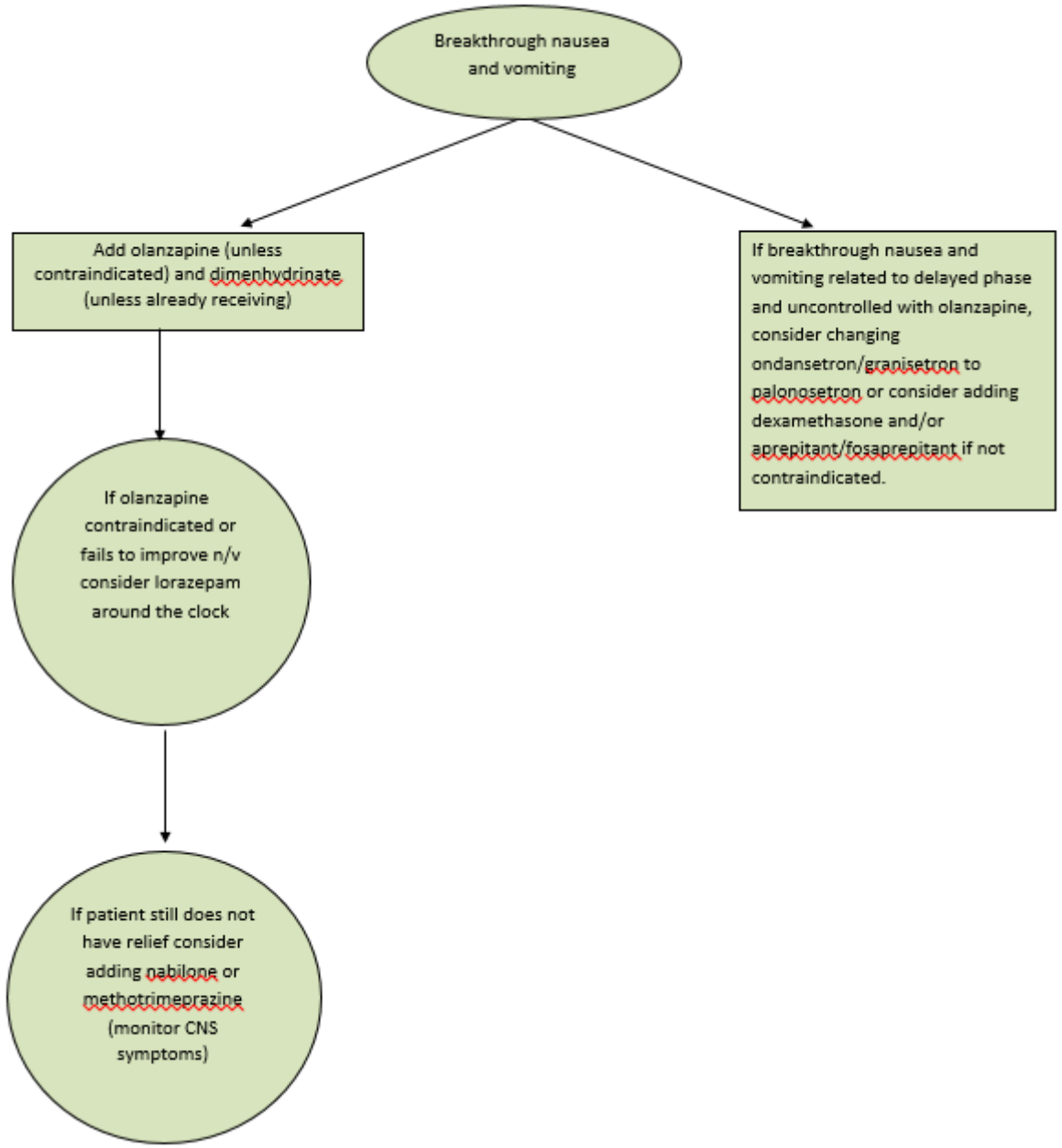
* For patients receiving cisplatin especially multiday chemotherapy or cisplatin or cyclophosphamide + anthracycline or high dose cyclophosphamide/ifosfamide/carboplatin consider prescribing palonosetron in place of ondansetron as palonosetron is more effective in the management of delayed nausea and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

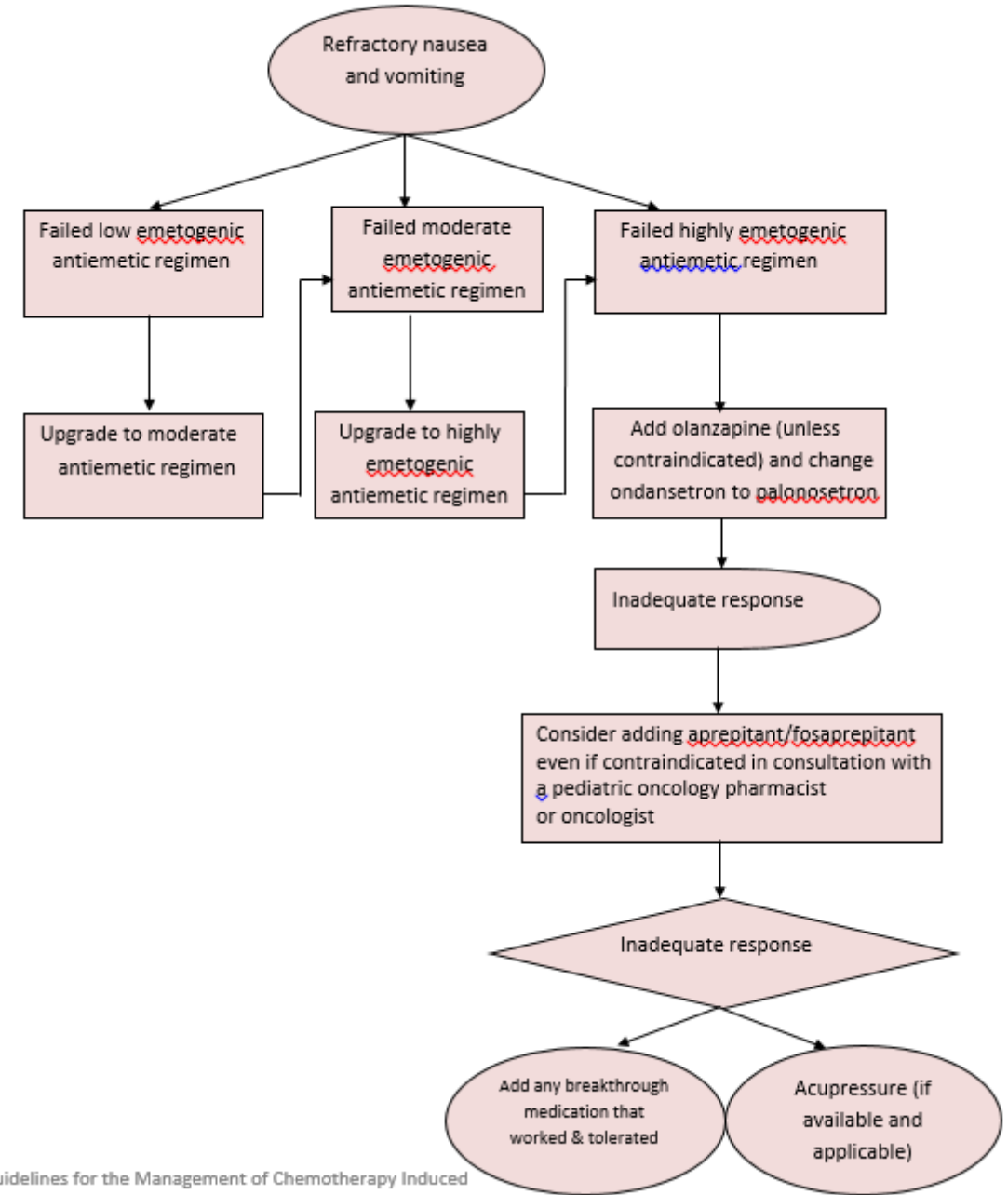
Antineoplastic Agents with HIGH Emetic Risk >90% frequency of emesis in absence of prophylaxis
Single agent antineoplastic therapy
Asparaginase (Erwinia) IV Carboplatin ≥ 175 mg/m²/dose Carmustine >250 mg/m²/dose Cisplatin Cyclophosphamide ≥ 1,500 mg/m²/dose Cytarabine ≥ 3 g/m²/dose Dactinomycin ≥ 0.045mg/kg/dose 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.

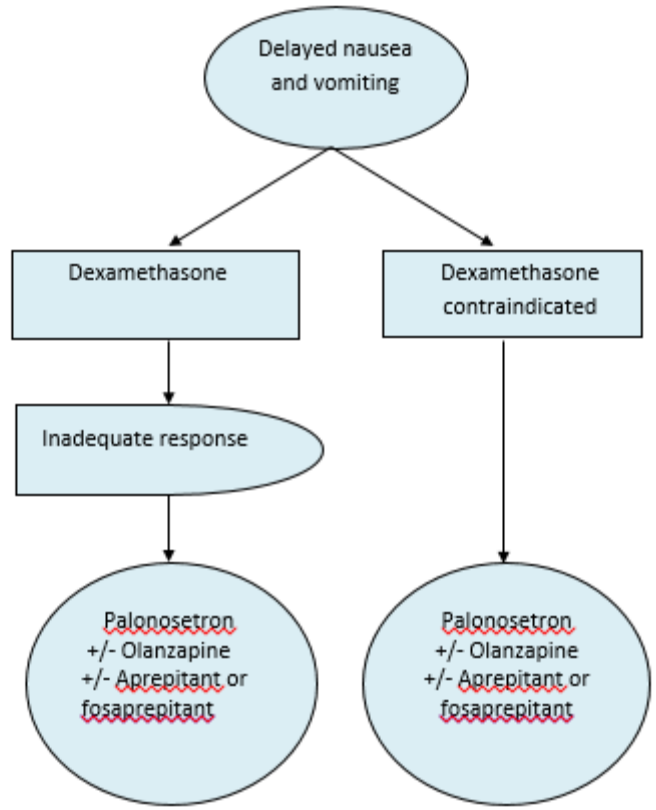
Algorithm 7: Management of Breakthrough Nausea and Vomiting During a Cycle of Chemotherapy



Algorithm 8: Management of Refractory Nausea and Vomiting



Algorithm 9: Management of Delayed Nausea and Vomiting



Algorithm 10: Management of Anticipatory Nausea and Vomiting

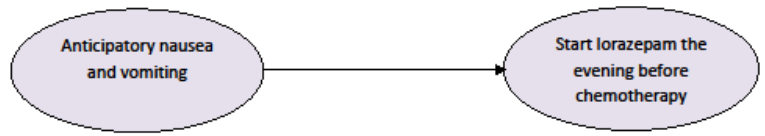


Table 1: Antiemetics, dosing and level of evidence for use

	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 Moderatly 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	Strong recommendation Moderate quality of evidence

		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	
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

Antiemetics recommendations for ORAL chemotherapy

Recommendation	Grade of recommendation
We recommend for children receiving **minimal to low** emetic potential chemotherapy: *Ondansetron or granisetron* pre-treatment	Weak
We recommend for children receiving **moderate to high** emetic potential chemotherapy: *Ondansetron or granisetron* pre-treatment and as needed	Strong

Antiemetic recommendation for **low and minimal** emetic parenteral chemotherapy:

Recommendation	Grade of recommendation
• We recommend that children receiving chemotherapy agents of low emetic risk receive: *ondansetron/granisetron*	Strong
• We recommend that children receiving chemotherapy agents of minimal emetic risk receive: *no routine prophylaxis*	Weak

Antiemetic recommendations for **moderately emetic** parenteral chemotherapy

Recommendation	Grade of recommendation
We recommend that children: (less than 6 months) • receiving moderately emetic chemotherapy receive: *Ondansetron/granisetron or palonosetron + dexamethasone*	Strong
• receiving moderately emetic chemotherapy who cannot receive dexamethasone receive: *Palonosetron*	Strong
We recommend that children: (6 months and older) • receiving moderately emetic chemotherapy: *Ondansetron/granisetron or palonosetron + dexamethasone*	Strong
• receiving moderately emetic chemotherapy which is NOT known or suspected tointeract with aprepitant/fosaprepitant and who cannot receive dexamethasone receive: *palonosetron + aprepitant/fosaprepitant*	Weak
• receiving moderately emetic chemotherapy which is known or suspected to interactwith aprepitant and who cannot receive dexamethasone receive: *Palonosetron*	Weak

Antiemetic recommendations for **highly emetic** parenteral chemotherapy

Recommendation	Grade of recommendation
We recommend that children: (less than 6 months) • receiving highly emetic chemotherapy receive: *Ondansetron/granisetron or palonosetron + dexamethasone*	Strong
• receiving highly emetic chemotherapy who cannot receive dexamethasone receive: *Palonosetron*	Strong
We recommend that children: (6 months and older) • receiving highly emetic chemotherapy which is NOT known or suspected to interact with aprepitant/fosaprepitant receive: *Ondansetron/granisetron or palonosetron + dexamethasone + aprepitant/fosaprepitant*	Strong
• receiving highly emetic chemotherapy which is known or suspected to interact with aprepitant/fosaprepitant receive: *Ondansetron/granisetron or palonosertron + dexamethasone*	Strong
• receiving highly emetic chemotherapy which is NOT known or suspected to interact with aprepitant/fosaprepitant and who cannot receive dexamethasone receive: *palonosetron + aprepitant/fosaprepitant*	Weak
• receiving highly emetic chemotherapy which is known or suspected to interact with aprepitant/fosaprepitant and who cannot receive dexamethasone receive: *Palonosetron*	Weak

Antiemetic recommendations for the management of **delayed** nausea and vomiting:

Recommendation	Grade of recommendation
• We recommend that children receiving chemotherapy with agents known to cause delayed nausea and vomiting (e.g., cisplatin, carboplatin (> 600 mg/m^2), anthracyclines (> 40 mg/m^2) and (cyclophosphamide + anthracycline) should receive: *Palonosetron + aprepitant/fosaprepitant (unless contraindicated) + dexamethasone (unless contraindicated)*	Weak
• We recommend that 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).	Weak
• We recommend for children 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 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.	Weak

Antiemetic recommendation for anticipatory and **refractory** nausea and vomiting::

Recommendation	Grade of recommendation
• We recommend that lorazepam may be used to prevent or treat **anticipatory CINV** in children.	Weak
• We recommend for children experiencing **breakthrough CINV**: Upgrade or escalate the acute CINV prophylaxis provided to that recommended for chemotherapy of the next higher emetic risk for children receiving acute CINV prophylaxis recommended for highly emetic chemotherapy: 1. Add olanzapine if not contraindicated 2. If olanzapine contraindicated or fails to work add lorazepam and if this does not work add either methotrimeprazine or nabilone or dimenhydrinate (if not already receiving). 3. If the nausea and vomiting thought to be delayed phase change ondansetron to palonosetron.	Weak
• We recommend for children experiencing **refractory CINV** and who are receiving acute CINV prophylaxis for minimally, low, or moderately emetic chemotherapy, clinicians should upgrade or escalate the acute CINV prophylaxis provided to that recommended for chemotherapy of the next higher level of emetic risk.	Weak
• We recommend for children experiencing **refractory CINV** and who are receiving acute CINV prophylaxis for highly emetic chemotherapy and who cannot receive olanzapine, we suggest that one of the following antiemetic agents be added to guideline-consistent CINV prophylaxis: 1. Change ondansetron to palonosetron 2. Consider adding aprepitant/fosaprepitant even if contraindicated (in consultation with the oncologist/pharmacist) 3. Add any breakthrough medication e.g., methotrimeprazine (also known as levomepromazine) or nabilone 4. Consider stimulation of Nei Gaun (P6) by means of acupressure or electroacupuncture	Weak

Non-pharmacologic management of CINV

Recommendation	Grade of recommendation
• Although beyond the scope of this guideline acupuncture, guided imagery, music therapy, progressive muscle relaxation and psycho-educational support and information may be of benefit in preventing acute CINV in children receiving chemotherapy agents.	Weak
We suggest that the following dietary interventions may be effective in preventing CINV: • 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 • Offering food while it is cold may help as cold food smells less • Avoid fried, fatty or spicy foods • Bland foods such as toast, crackers, potatoes, rice, vegetables, and easily digested meats (chicken) are often better tolerated • When nausea/vomiting is present, do not pressure the child to eat, they may acquire a learned aversion to certain foods • Reduce food aromas and other stimuli with strong odors	Weak

Questions?