Provincial Clinical Knowledge Topic
Chemotherapy Induced Nausea and Vomiting, Pediatric – Inpatient
V 1.0

Document History

Version	Date	Description of Revision	Revised By
1.0	October 2017	Document Complete	Jennifer Jupp

Important Information Before you Begin

The recommendations contained in this knowledge topic have been provincially adjudicated and are based on best practice and available evidence. Clinicians applying these recommendations should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care. This knowledge topic will be reviewed periodically and updated as best practice evidence and practice change.

The information in this topic strives to adhere to Institute for Safe Medication Practices (ISMP) safety standards and align with Quality and Safety initiatives and accreditation requirements such as the Required Organizational Practices. Some examples of these initiatives or groups are: Health Quality Council Alberta (HQCA), Choosing Wisely campaign, Safer Healthcare Now campaign etc.

This topic is based on the following guidelines:

Pediatric Oncology Group of Ontario (POGO): Guideline for Classification of the Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Cancer Patients.

Pediatric Oncology Group of Ontario (POGO): Guideline for the Prevention of Acute Nausea and Vomiting Due to Antineoplastic Medication in Pediatric Cancer Patients.

Patel P, Robinson PD, Thackray J, et al. Guideline for the prevention of acute chemotherapy-induced nausea and vomiting in pediatric cancer patients: a focused update. Pediatr Blood Cancer. 2017;00:e26542.

Pediatric Oncology Group of Ontario (POGO): Guideline for the Prevention and Treatment of Anticipatory Nausea and Vomiting due to Chemotherapy in Pediatric Cancer Patients.

Pediatric Oncology Group of Ontario (POGO): Guideline for the Treatment of Breakthrough and the Prevention of Refractory Chemotherapy-Induced Nausea and Vomiting in Children with Cancer.

2016 MASCC/ESMO Consensus Recommendations: Prevention of Acute Chemotherapy-Induced Nausea and Vomiting in Children.

Rationale

Antineoplastics can lead to nausea and vomiting in up to 70% of pediatric patients.[1] Patients experiencing nausea and vomiting as a result of anticancer therapy suffer from a reduction in quality of life, inability to continue with daily activities, nutritional deficits and non-adherence to therapy. Many pediatric survivors report Chemotherapy/Antineoplastic Induced Nausea and Vomiting (CINV) as an important factor in their quality of life during treatment and although vomiting may improve during therapy, nausea may worsen.

Due to the high incidence of CINV in pediatric patients, it is essential that adequate prophylactic antiemetics be provided for all patients at the beginning of their chemotherapy course. Optimizing CINV therapy throughout the chemotherapy course is also important to reduce the risk of delayed, anticipatory and refractory CINV. The recommendations in this document will serve to guide health care providers in the prevention and treatment of CINV in pediatric oncology patients.

Reference to 'chemotherapy' in this document includes all antineoplastic agents used for treatment of cancer.

CINV may be classified as follows:

- Acute: occurring within the first 24 hours of chemotherapy administration
- Delayed: occurring 24 hours to 7 days after the last dose of chemotherapy administered
- Anticipatory: a conditioned response that leads to CINV prior to chemotherapy administration
- Breakthrough: CINV occurs when patients experience CINV in the acute or delayed phase despite appropriate CINV prophylactic antiemetics
- Refractory: CINV occurs when CINV is uncontrolled in the acute or delayed phase in a previous cycle of chemotherapy (patient received breakthrough CINV treatment)

In 2011, the Pediatric Oncology Group of Ontario (POGO) published a series of guidelines with recommendations for Emetogenicity Classification and the Prevention and Treatment of Acute, Anticipatory, Breakthrough and Refractory CINV.[2,3,4,5] These guidelines serve as the foundational documents for the recommendations in this document.

CLASSIFYING EMETOGENICITY

The Guideline for the Classification of the Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Cancer Patients,[2] served as the first evidence-based guideline for the classification of emetogenicity specifically for pediatric patients. Previous to this guideline, emetogenicity was classified using adult data. The POGO Emetogenicity Guideline provides an important tool for health care providers in the assessment of the emetogenicity of chemotherapy for children aged 1 month to 18 years. It is important to note that this guideline is limited to the assessment of chemotherapy emetogenicity in the acute phase (within 24 hours of administration of a chemotherapeutic agent) in pediatric patients naïve to chemotherapy. Its scope does not include anticipatory, breakthrough or delayed phase CINV, or nausea and

vomiting that is related to radiation therapy, disease, co-incident conditions or end-of-life care. A recent guideline update by Multinational Association of Supportive Care in Cancer (MASCC) and European Society for Medical Oncology (ESMO) provided emetogenicity rating recommendations for newer chemotherapeutic agents, including oral agents.[6] The MASCC ratings are based on adult data and in the absence of pediatric data, it is recommended these ratings be used to guide emetogenicity for agents not classified on the 2011 POGO Emetogenicity Guideline.

Four categories of emetogenic potential, based on expected rates of CINV[2] exist and are widely accepted by many oncology groups:

- Highly Emetogenic Chemotherapy (HEC): CINV occurs in greater than 90% of patients
- Moderately Emetogenic Chemotherapy (MEC): CINV occurs in 30-90% of patients
- Low Emetogenic Chemotherapy (LEC): CINV occurs in 10-30% of patients
- Minimal Emetogenic Chemotherapy: CINV occurs in less than 10% of patients

Multiple Day Chemotherapy:

- The emetogenicity of multiple day chemotherapy should be classified based on the emetic risk of the most highly emetogenic agent on each day of chemotherapy. As many pediatric oncology regimens are multiple days in length, it is important to assess emetogenicity on an ongoing basis as antiemetic requirements may change throughout the course.

Combination Chemotherapy:

- The emetogenicity of the regimen should be based on the agent with the highest emetic risk, except for the combinations as listed in the POGO guidelines (Table 9 and Table 10). These combinations have been shown to have a higher emetic risk than ranking the agents alone and should be considered HEC.

It should be noted that nausea reporting in the literature, for pediatric oncology patients, is inconsistent and often reported without the use of a validated nausea assessment tool. Nausea is also frequently reported in combination with emesis, thus the true extent of nausea occurrence in pediatric oncology patients remains largely unknown.

See Appendix A and Appendix B for Emetogenicity Tables.

ANTIEMETIC RECOMMENDATIONS:

These guidelines have adapted the POGO guidelines for the prevention and treatment of acute, anticipatory, breakthrough and refractory CINV.

KEY POINTS:

- Suboptimal antiemetic management may lead to acute CINV and anticipatory CINV in subsequent cycles.
- Antiemetic therapy should take into account the inherent emetogenicity of the chemotherapeutic agents and the patient's prior history with chemotherapy. CINV

control for previous cycles should be assessed, prior to prescribing for subsequent cycles.

HEC ANTIEMETIC PROPHYLAXIS RECOMMENDATIONS

Table 1. Patients greater than or equal to 6 months of age receiving HEC	
Patients with no known or suspected drug interactions with aprepitant and can receive dexamethasone	ondansetron or granisetron **PLUS** dexamethasone **PLUS** aprepitant
Patients with known or suspected drug interactions with aprepitant	ondansetron or granisetron **PLUS** dexamethasone
Patients who cannot receive dexamethasone	ondansetron or granisetron **PLUS** aprepitant

Studies in the 1990s have shown the use of serotonin-type 3 (5-HT3) receptor antagonists to be more effective than traditional antiemetics, such as metoclopramide and chlorpromazine (even when combined with dexamethasone).[7] The use of first generation 5-HT3 receptor antagonists (ondansetron and granisetron) have shown comparable complete responses for CINV, with rates varying between 23-72% in patients receiving highly emetogenic chemotherapy.[6] Pooled analysis, from a recent systematic review, reported no differences in efficacy between ondansetron and granisetron.[7] Reports of improved efficacy with the addition of a corticosteroid to a 5HT3 receptor antagonist is limited in the pediatric oncology setting, however, a randomized controlled trial examining the use of ondansetron with dexamethasone, indicated that combined therapy resulted in a higher rate of complete vomiting control when compared to ondansetron alone.[3] This was supported by a meta-analysis which reported that the addition of a corticosteroid to a 5HT3 antagonist resulted in a relative risk of complete control of vomiting of 2.03 (95% CI:1.35-3.04). Ondansetron and granisetron are both available on the AHS Formulary, with ondansetron as the preferred first line agent. Palonosetron is currently not listed as a formulary alternative, but does appear as a recommendation in both adult and pediatric clinical practice guidelines. Future consideration for the use of palonosetron can be made if the formulary status changes.

There is minimal data regarding use of triple antiemetic therapy with aprepitant, dexamethasone and a 5HT3 receptor antagonist in pediatric oncology patients. Based on recent pediatric data, the POGO guideline update included aprepitant (a substance P/neurokinin 1 receptor inhibitor).[8] MASCC guidelines strongly recommend combination therapy with ondansetron, dexamethasone and aprepitant for adult and pediatric cancer patients.[6]

For patients where dexamethasone is not recommended, POGO guidelines recommend double antiemetic therapy with aprepitant and a 5HT3 receptor antagonist. Literature is scant to support the use of aprepitant without dexamethasone except for one trial which had an unknown number of pediatric patients who received a 5HT3 antagonist with/without dexamethasone and aprepitant that showed higher vomiting complete control rates when compared to those that did not receive aprepitant.[8]

Aprepitant is not recommended for use in children less than 6 months of age as it has not been studied in this group. The following are antiemetic prophylaxis guidelines for patients less than 6 months in age.

Table 2. Patients less than 6 months of age receiving HEC	
Patients with no dexamethasone contraindications	ondansetron or granisetron **PLUS** dexamethasone
Patients that cannot receive dexamethasone	ondansetron or granisetron

NOTE: Considerations for prescribing aprepitant or dexamethasone should be evaluated and risk versus benefit assessed. See 'Other Drug Therapy Considerations'.

MEC ANTIEMETIC PROPHYLAXIS RECOMMENDATIONS

Table 3. Patients receiving MEC	
Patients with no dexamethasone contraindications	ondansetron or granisetron **PLUS** dexamethasone
Patients with no known or suspected drug interactions with aprepitant, greater than or equal to 6 months of age and cannot receive dexamethasone	ondansetron or granisetron **PLUS** aprepitant

Cannot receive dexamethasone, less than 6 months of age, known or suspected drug interactions with aprepitant	ondansetron or granisetron

The literature provides little guidance for recommendations for pediatric oncology patients receiving MEC. POGO guideline recommendations for a 5HT3 receptor antagonist in combination with corticosteroid for MEC CINV prophylaxis are based on a trial which included 428 children administered ondansetron and dexamethasone where complete control was reported as 78-81% and 70-73% for vomiting and nausea respectively.[2] The recommendation is consistent with adult guidelines that suggest double antiemetic therapy with a 5HT3 receptor antagonist and steroid for patients receiving MEC.

Given the broad range of CINV risk in this emetogenicity category (30-90% risk), considerations can be made for some patients to escalate to HEC recommendations and the addition of aprepitant to the antiemetic regimen for these patients may be warranted.

NOTE: Considerations for prescribing aprepitant or dexamethasone should be evaluated and risk versus benefit assessed. See 'Other Drug Therapy Considerations'.

LEC ANTIEMETIC PROPHYLAXIS RECOMMENDATIONS

Table 4. Patients receiving LEC	
Patients receiving LEC	ondansetron or granisetron

POGO guideline recommendations for LEC are supported by a synthesis of studies which indicated that CINV control rates of 74% can be obtained with a 5HT3 receptor antagonist alone.[3]

MINIMAL ANTIEMETIC PROPHYLAXIS RECOMMENDATIONS

RECOMMENDATION: No antiemetic therapy required

POGO recommendations were based on adult data indicating no antiemetic prophylaxis is required for chemotherapy within this emetogenicity category.[3]

OTHER DRUG THERAPY CONSIDERATIONS:

5HT3 ANTAGONISTS AND CARDIAC EFFECTS:

Abnormal cardiac electrical activity (prolongation of PR and QT intervals) have been reported in healthy adult patients administered 5HT3 receptor antagonists.[9,10] In these patients, small, reversible, clinically insignificant, asymptomatic changes in ECG readings were noted, in addition to changes in heart rates.[10] Pinarli described similar changes in 38 pediatric oncology

patients, where minor changes to ECG parameters occurred after 5HT3 receptor antagonist and chemotherapy (including anthracyclines) administration and concluded that neither dangerous rhythm disturbances nor serious ECG changes were noted.

ECG changes may be reversible and asymptomatic, but may also lead to potentially fatal cardiac arrhythmias (e.g. Torsades de pointes). Patients with underlying cardiac diseases, congestive heart failure, bradycardia, electrolyte disturbances and those patients that are administered other medications that can lead to QT prolongation (e.g. olanzapine) are at higher risk for this adverse effect. Routine ECG monitoring may be recommended for patients with the above risk factors and changes to drug therapy may need to be considered.[9]

APREPITANT PHARMACOKINETIC INTERACTIONS:

Aprepitant is a moderate CYP3A4 inhibitor and a weak CYP2C9 inducer. A recent systematic review of aprepitant drug interactions, using the United States Food and Drug Administration (FDA) definition for clinically significant pharmacokinetic interactions, concluded the following agents exhibited clinically signification pharmacokinetic drug interactions with aprepitant: bosutinib, cabazitaxel, cyclophosphamide, dexamethasone, methylPREDNISolone, midazolam, oxyCODONE, and tolBUTamide.[11] Aprepitant interactions with these drugs lead to a maximum concentration (Cmax) and area under the concentration versus time curve (AUC) difference that was greater than 1.25 or less than 0.8 (FDA definition for clinically significant drug interactions) or if other pharmacokinetic parameters were altered (e.g. reduced clearance). Pharmacokinetic parameters were also altered for the following agents, but did not lead to differences in AUC or Cmax: dexamethasone IV, erlotinib, ifosfamide IV, QUEtiapine PO, pazopanib PO, PARoxetine PO, tacrolimus IV and thiotepa IV. Although pharmacokinetic changes can occur with aprepitant co-administration with the above listed medications, not all can be correlated to clinically significant effects. Caution should be used when medications that are substrates of CYP3A4 and CYP2C9 are used concurrently with aprepitant. Information for some specific agents are drawn from the literature and presented below.

DEXAMETHASONE

Aprepitant may reduce dexamethasone clearance by 25-50% and may increase possible adverse effects associated with additional steroid exposure. A dose reduction of dexamethasone by 50% is routinely recommended.[11] It should be noted that in these AHS guidelines, consensus on dexamethasone dose was reached and the recommended dose for antiemetic prophylaxis is lower than that recommended in POGO or adult guidelines. Hence, due to the lower dose, the working group felt no further reduction of dexamethasone was warranted for daily maximum doses of 12 mg (see order set for dosing recommendations). For higher doses, dexamethasone should be reduced by 50% when co-administered with aprepitant.

CYCLOSPHOSPHAMIDE

The use of cyclophosphamide and aprepitant warrants discussion. Cyclophosphamide is a pro-drug and requires hydroxylation by CYP3A4 to its active metabolite for antitumor activity. CYP3A4 also leads to dechloroethylation of cyclophosphamide to neurotoxic

and nephrotoxic compounds.[12] Changes in AUC and Cmax have been noted in one report, but not others.[11] Considerable interpatient variability is noted in the literature and changes in efficacy or toxicity have not been noted and are not likely to be clinically significant.

CYP3A4 substrates which are also substrates of p-glycoprotein or other efflux transporters have not been reported to lead to significant changes in pharmacokinetic disposition, likely due to the elimination of these agents via an alternative pathway.[11]

ADVERSE EVENTS ASSOCIATED WITH APREPITANT

Adverse events associated with concurrent administration with aprepitant have been reported in the literature, without evidence of pharmacokinetic changes. Patel et al, examined the probability of adverse effects associated with co-administration of aprepitant.[11] In this report, an adverse event was defined as an event where a patient experienced discomfort, harm, or changes in laboratory parameter that was indicative of an increased risk of harm that was highly suspected to have occurred due to co-administration with aprepitant. Relevant adverse effects were noted when aprepitant was co-administered with the following agents: alcohol, ifosfamide, oxyCODONE, QUEtiapine, selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors and warfarin.[11] Co-administration of aprepitant with these agents should be done with caution and with appropriate monitoring. Description of the adverse effects reported in the literature are listed below:

Table 5. Adverse effects associated with aprepitant drug interactions[11]

Drug	Description of Adverse Effect
alcohol	Impaired cognition
ifosfamide	Neurotoxicity
oxyCODONE	Decreased respiratory rate, increased feeling of a ‘high’
QUEtiapine	Somnolence
selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors	Vomiting
warfarin	INR changes
tacrolimus, sirolimus	Levels may increase
oral contraceptives	Reduced efficacy

IFOSFAMIDE

The interaction with ifosfamide is inconsistently reported in the literature. No reports in the literature for the co-administration of ifosfamide and aprepitant met the FDA definition for clinically significant drug interactions. However, there have been various conflicting reports noting ifosfamide encephalopathy from the co-administration of aprepitant. Caution and close monitoring are recommended.[12]

IMMUNOSUPPRESSANTS

Although it is difficult to confirm a direct correlation to concurrent aprepitant use, increases in tacrolimus and sirolimus levels have been noted. Monitor levels closely when these medications are co-administered.[11,12]

FEBRILE NEUTROPENIA

A recent meta-analysis published by Okumura et al. indicated that aprepitant did not increase the risk of febrile neutropenia.[13] Patients were aged 6 months to 19 years and were treated for bone cancers, Ewings Sarcoma, rhadomyosarcoma, Hodgkins lymphoma and other solid tumors with moderate to highly emetogenic chemotherapy. This report showed a 52% reduction in chemotherapy induced vomiting occurrence with no additional risk for febrile neutropenia when aprepitant was administered. It should be noted that infection was not well documented in any of the included randomized controlled trials, differing doses of aprepitant and dexamethasone were used and acute myeloid leukemia patients were also not included.

Evaluation of drug interactions with aprepitant should be reviewed prior to initiation of therapy. If a significant drug interaction precludes the use of aprepitant, see recommendations above in Table 1 and Table 3 for alternatives. Above information may not include all relevant drug interactions with aprepitant. Patients co-administered CYP3A4 and CYP2C9 substrates should be assessed for potential risk for pharmacokinetic changes or increased risk for adverse effects.

USE OF DEXAMETHASONE FOR CINV PROPHYLAXIS

Dexamethasone is the most frequently used steroid for CINV prophylaxis. No trials directly compared different types of steroids, dosing, schedules or routes of administration. The use of dexamethasone with 5HT3 receptor antagonists lead to better CINV control, but its use is not recommended in many pediatric oncology protocols, (e.g. leukemia, brain tumors) due to concerns regarding potential interference with apoptosis, fungal infection and distribution of chemotherapy across the blood-brain-barrier.[4]

BRAIN TUMORS

Pre-clinical studies suggest the use of steroids may reduce the effectiveness of chemotherapy to some cancers.[7] However, no reports in the literature have found an association between steroids, used as an antiemetic, leading to worsened outcomes. The risks and benefits of steroid use in brain tumor patients should be evaluated prior to initiation and specific protocol recommendations adhered to.

INFECTION RISK IN ACUTE MYELOID LEUKEMIA PATIENTS

Steroid duration has been implicated in increasing infectious complications in pediatric patients with acute myeloid leukemia. In a retrospective study, Dix et al reported rates of 24.5%, 7.6% and 1.3% of sterile site microbiologically documented infection, sepsis and death respectively.[14] Although it is unclear whether steroids were used for CINV

prophylaxis in this report, the duration of steroid use was a significant factor associated with death.

Antiemetic doses of dexamethasone have been reported in the literature to range from 6-24 mg/m^2/day.[3] As the association between steroid dose and infection remains unclear and clinical experience indicates that patients experience adverse effects at higher doses, this guideline did not adopt the POGO recommendations for a dexamethasone dose of 6 mg/m^2/dose IV/PO every 6 hours. The starting antiemetic dose recommendation, in these AHS guidelines, is arbitrary and guidance is provided to escalate doses up to a maximum of 5 mg/m^2/dose IV/PO every 6 hours or a daily maximum of 16 mg/day (see order set). In adult guidelines, doses up to 12 mg/day do not require adjustment when given concurrently with aprepitant,[9] therefore this guideline recommends dosage reduction of 50% for dexamethasone doses of >12mg/day.

DELAYED NAUSEA AND VOMITING

CINV outcome data are rarely reported beyond the first 24 hours of chemotherapy administration, therefore little guidance is available for the prevention and treatment of delayed CINV in pediatric oncology patients.[7] Delayed CINV may occur within 24 hours to 5 to 7 days from the administration of the last dose of chemotherapy. The optimal antiemetic duration after chemotherapy remains unclear. Studies in pediatric patients have provided antiemetic therapy for 2-3 days after the last dose of chemotherapy administration, with little information on effectiveness. Adult CINV guidelines recommend the use of antiemetics for 2 to 4 days after the last dose of chemotherapy.[9] There are no randomized trials available for review and optimal prophylaxis of delayed CINV remain a research gap. Most adult and pediatric guidelines recommend optimizing acute phase antiemetics to reduce the incidence of delayed CINV.[5] The following has been used in some pediatric and adult centers:

- Administer appropriate antiemetics for each day of chemotherapy administration (acute phase) and consider continuing for 2 to 4 days after the last dose for agents known to cause delayed CINV (cisplatin, cyclophosphamide, ifosfamide, anthracyclines, carboplatin).[6,9]
- 5HT3 antagonists and dexamethasone have been used alone or in combination in adult patients and can be considered in pediatric patients.[9,15]

BREAKTHROUGH CINV

Breakthrough CINV occurs when patients experience CINV in the acute or delayed phase despite appropriate CINV prophylactic antiemetics.

Table 6. Recommendations for breakthrough CINV[3]

Antiemetic Regimen	Recommendation
For patients currently receiving antiemetic prophylaxis for HEC	Add olanzapine (see order set for dosing) to current antiemetic regimen

For patients receiving antiemetic prophylaxis for HEC and cannot receive olanzapine	Add metoclopramide (patients greater than1 year of age) to current antiemetic regimen; consider diphenhydramine co-administration to reduce the risk of extrapyramidal symptoms. Avoid using metoclopramide with olanzapine.
For patients currently receiving antiemetic prophylaxis for MEC, LEC or minimal emetogenic chemotherapy	Escalate antiemetic therapy to the next higher level of emetogenic risk

The recommendation to escalate antiemetic therapy to the next level of emetogenicity risk is based largely on the assumption that an antiemetic regimen used for higher emetogenicity would be more effective.[5] No pediatric or adult literature is available to validate this recommendation, but escalating therapy is likely safe and effective.

Olanzapine: The addition of olanzapine to the existing antiemetic regimen is consistent with adult guidelines, where it has been shown in clinical trials to be effective for nausea and for breakthrough CINV. One retrospective report examined the use of olanzapine in children undergoing chemotherapy, where complete vomiting control was achieved in 57% of chemotherapy blocks, although nausea was not assessed.[19] Oral doses in this report ranged from 0.03-0.3 mg/kg/dose, with a mean dose of 0.1 mg/kg/dose. For those patients not experiencing optimal control and no adverse effects, Flank et al, have suggested increasing doses up to 0.14 mg/kg/dose. Adverse effects such as sedation can be reduced by decreasing the dose of olanzapine. A systematic review of adverse effects associated with olanzapine indicated that weight gain and sedation occurred most frequently (78% and 48% respectively), while extrapyramidal symptoms and ECG abnormalities were reported as 9%.[8] Most adverse effects associated with olanzapine were minor in clinical significance and no fatalities were attributed to the use of olanzapine. Olanzapine injection has not been studied in the setting of CINV in adults or pediatric patients and should be avoided. Avoid the use of metoclopramide with olanzapine as this combination has been associated with neuroleptic malignant syndrome and extrapyrimidal reactions.[20]

Cannabinoids: Such as nabilone have been used previously in this patient population and are likely effective. Cannabinoids have been associated with sometimes intolerable adverse effects, such as sedation, dizziness, mood alteration and hallucinations.[7] See order set for dosing recommendations.

Dimenhydrinate: Although dimenhydrinate has been routinely used for the treatment of breakthrough CINV, its use has not been reported in the literature to be effective. Adverse effects associated with dimenhydrinate can also be bothersome. Dimenhydrinate was not included in these guidelines or order sets for these reasons.

REFRACTORY CINV

Refractory CINV occurs when CINV is not adequately controlled in the acute or delayed phase in a previous cycle of chemotherapy (patient received breakthrough CINV treatment).

Table 7. Recommendations for refractory CINV

Antiemetic Regimen	Recommendation
For patients currently receiving antiemetic prophylaxis for HEC	Consider changing ondansetron to granisetron. Consider adding aprepitant for patients that had not previously received aprepitant. Consider adding olanzapine if patient has received aprepitant previously.
For patients currently receiving antiemetic prophylaxis for MEC, LEC or minimal emetogenic chemotherapy	Escalate antiemetic therapy to the next higher level of emetogenic risk
For patients receiving antiemetic prophylaxis and the above recommendations are ineffective	Consider using breakthrough CINV interventions • Add olanzapine • Add metoclopramide (patients greater than 1 year of age) to current antiemetic regimen; consider diphenhydramine co-administration to reduce the risk of extrapyramidal symptoms • Acupressure or acupuncture Consult psychology, GI

Switching from ondansetron to granisetron: There is no clear evidence that one 5HT3 receptor antagonist is more efficacious than the other. Ondansetron is the AHS formulary preferred agent and thus, should be used as first line. Ondansetron is primarily metabolized by CYP2D6 and studies in adults have shown that genetic polymorphisms could lead to rapid ondansetron metabolism and thus, less effective CINV control.[5] In the only adult study examining this issue, 47% of patients receiving HEC achieved complete CINV control (no vomiting and no or mild nausea) after switching to granisetron, compared to 5% for those patients that remained on ondansetron. Therefore, if patients experience CINV control failure with ondansetron, the AHS formulary alternative, granisetron may be prescribed. Granisetron should also be used for subsequent cycles for these patients.

Aprepitant: Aprepitant can be considered in those patients that were previously not prescribed aprepitant due to a known or suspected drug interaction. Robust evidence for clinically significant drug interactions with concurrent administration with aprepitant remain largely unavailable (see Other Drug Therapy Considerations) and the risk of toxicity should be weighed against optimal CINV control.

Acupressure or acupuncture has been used in adult patients with reported complete vomiting control rates of 68% and 37% respectively.[5]

ANTICIPATORY CINV:

CINV prevention is key. Antiemetic therapy must be optimized during the acute and delayed CINV phases with the first cycle to prevent anticipatory CINV in subsequent cycles. A recent systematic review of antiemetic medication for prevention and treatment of CINV, provided no additional guidance for anticipatory CINV and loazepam and psychosocial interventions continued to be recommended.[7]

- lorazapam can be used to prevent or treat anticipatory CINV. If lorazepam is used for anticipatory CINV, prophylaxis should start the night prior to chemotherapy administration. See order set for recommended dosing.
- Psychological interventions such as hypnosis or systematic desensitization may be offered to patients with anticipatory CINV.[2]

Goals of Management

GOAL: Optimal control of Chemotherapy/Antineoplastic Induced Nausea and Vomiting (CINV) in the acute, delayed and anticipatory phases of chemotherapy administration.

- Appropriate prophylactic antiemetics should be prescribed to minimize nausea, vomiting or the use breakthrough medications in any phase of chemotherapy administration.
- It is essential to include the patient and caregivers, when appropriate, to ensure their values can be incorporated into the decision making process[5].

Clinical Documentation

Assessment

- Rule out other causes of nausea and vomiting.[17]
    - Non-chemotherapy medications: (e.g. opioids)
    - Central Nervous System (CNS): CNS tumors, raised intracranial pressure
    - Gastrointestinal (GI): gastritis, constipation, intestinal obstruction, abdominal tumors
    - Infections
    - Metabolic abnormalities
    - Anxiety

Documentation

- Emesis: accurate documentation of frequency of emetic episodes is recommended
- Nausea: Nausea can be assessed utilizing the Pediatric Nausea Assessment Tool (PeNAT).[18] See Appendix C for PeNAT Tool.
    - The PeNAT should be completed by the patient twice daily for the entire chemotherapy cycle.
    - The PeNAT script:
        - Recommended as it will assist the health care provider to determine whether the patient understands that nausea is being assessed.
        - Should be administered by a health care provider once at the beginning of each chemotherapy cycle.
        - Parents should be taught how to administer the PeNAT to the child.
        - Some patients will require the PeNAT script read more than once in a cycle.
    - The patient should use the PeNAT to describe how nauseated they are feeling at the moment the test is administered. It cannot be used retrospectively.
    - Do not use the PeNAT if the child is unwilling or unable to participate or if the patient does not understand the concept of nausea. Responses to the PeNAT must come from the child, not the parent.
    - PeNAT scores should be documented in the health record.
    - Optimization of antiemetics should occur after reviewing daily PeNAT scores.
    - Recommend that a report trending PeNat scores and antiemetics be available to bedside clinicians.
- Documentation of the antiemetic regimen used for the current cycle should be included in the patient's health record (e.g. medication administration record, progress notes or discharge summary).

Decision Making

- Antiemetics appropriate to the emetogenic classification should be prescribed and administered prior to the first dose of chemotherapy and continued on a scheduled basis throughout the chemotherapy course. See CLASSIFYING EMETOGENICITY and Appendix A for guidance.
- Considerations for subsequent cycles:
    - Assess efficacy of antiemetic therapy during the prior cycle (if chemotherapy similar). Review:
        - Antiemetic agents used
        - Patient's CINV history
        - PeNAT scores
    - Determine emetogenicity of current cycle
    - Prescribe antiemetics appropriate for the level of emetogenicity (HEC, MEC, LEC, minimal)
    - Alterations in prophylatic antiemetic regimen should occur for patients that experience incomplete control with a subsequent cycle. (see Refractory CINV)

Medication Recommendations

Key Points:

- Antiemetic prophylaxis should be provided:
    - 60 minutes prior to chemotherapy if using oral antiemetic agents
    - 30 minutes prior to chemotherapy if using intravenous antiemetic agents
- Doses of antiemetics should be given on a regular schedule (e.g. not PRN) regardless of whether the patient is experiencing nausea or vomiting and continue for 24 to 48 hours following last dose of chemotherapy. See DELAYED NAUSEA AND VOMITING for recommendations for chemotherapy with a higher risk of delayed nausea and vomiting.

*ondansetron is currently the AHS Formulary Alternative; granisetron can be used in those patients failing ondansetron or previously stabilized on granisetron

Name of Order Set: Pediatric Chemotherapy Induced Nausea and Vomiting Orders

Order Set Components

Order Set Keywords: cancer, oncology, chemotherapy, nausea, vomiting, antiemetics, emesis
Order Set Requirements: Body Surface Area

Patient Care

☐ Monitor nausea using Pediatric Nausea Assessment Tool (PeNAT) BID

Medications

**ondansetron is currently the preferred AHS Formulary Agent; granisetron can be used in those patients failing ondansetron or previously stabilized on granisetron*

For Low Emetogenic Chemotherapy (LEC):

☐ ondansetron _____ mg (0.15 mg/kg/dose or 5 mg/m^2/dose; *maximum dose 8 mg*) IV/PO once prior to chemotherapy; **and then** ondansetron _____ mg (0.15 mg/kg/dose or 5 mg/m^2/dose; *maximum dose 8 mg*) every 8 hours PRN for breakthrough nausea/vomiting. Start 30 minutes prior to chemotherapy if using IV antiemetic or 60 minutes prior to chemotherapy if using PO antiemetic.

OR

Only for patients uncontrolled on ondansetron **or** previously stabilized on granisetron:

☐ granisetron _____ mg (0.02 to 0.04 mg/kg/dose) IV/PO once prior to chemotherapy **and then** granisetron _____ mg (0.02 to 0.04 mg/kg/dose) every 12 hours PRN for breakthrough nausea/vomiting. Start 30 minutes prior to chemotherapy if using IV antiemetic or 60 minutes prior to chemotherapy if using PO antiemetic.

For Moderate Emetogenic Chemotherapy (MEC):

☐ ondansetron _____ mg (0.15 mg/kg/dose or 5 mg/m^2/dose; *maximum dose 8 mg*) IV/PO every 8 hours. Start 30 minutes prior to chemotherapy if using IV antiemetic or 60 minutes prior to chemotherapy if using PO antiemetic.

OR

Only for patients uncontrolled on ondansetron **or** previously stabilized on granisetron:

☐ granisetron _____ mg (0.02 to 0.04 mg/kg/dose) IV/PO every 12 hours. Start 30 minutes prior to chemotherapy if using IV antiemetic or 60 minutes prior to chemotherapy if using PO antiemetic.

AND

☐ dexamethasone _____mg (2.5 mg/m^2/dose) IV/PO every 12 hours. Start 30 minutes prior to chemotherapy if using IV antiemetic or 60 minutes prior to chemotherapy if using PO antiemetic.

OR

☐ dexamethasone _____mg IV/PO every _____ hours. Start 30 minutes prior to chemotherapy if using IV antiemetic or 60 minutes prior to chemotherapy if using PO antiemetic. (*Dose and/or frequency may be increased on a case-by-case basis to a maximum of 5 mg/m^2/dose PO/IV every 6 hours or a daily maximum of 16 mg. Doses up to 12 mg/day of dexamethasone do not require adjustment when given concurrently with aprepitant.)*

OR

If unable to administer dexamethasone:

☐ aprepitant _____ mg PO once 60 minutes prior to chemotherapy on Day 1 **and then** aprepitant _____ mg PO once daily for two doses and then reassess. *(Use table below to guide ordering)*

Patient age/ Body weight	aprepitant Dose for Day 1	aprepitant Dose for Days 2 and 3
Age 6 months to less than 12 years **AND** weigh between 6 and less than 30 kg	3 mg/kg (*maximum dose 125 mg/dose*)	2 mg/kg (*maximum dose 80 mg/dose*)
	Round dose of suspension to the nearest 10 mg	
Age 12 years or older **OR** weigh at least 30 kg	125 mg	80 mg

For High Emetogenic Chemotherapy (HEC):

**ondansetron is currently the preferred AHS Formulary Agent; granisetron can be used in those patients failing ondansetron or previously stabilized on granisetron*

☐ aprepitant _____ mg *(Use table below to guide ordering)* PO once 60 minutes prior to chemotherapy on Day 1 **and then** aprepitant _____ mg *(Use table below to guide ordering)* PO once daily for two doses and then reassess.

Patient age/ Body weight	aprepitant Dose for Day 1	aprepitant Dose for Days 2 and 3
Age 6 months to less than 12 years AND weigh between 6 and less than 30 kg	3 mg/kg (*maximum dose 125 mg/dose*)	2 mg/kg (*maximum dose 80 mg/dose*)
	Round dose of suspension to the nearest 10 mg	
Age 12 years or older OR weigh at least 30 kg	125mg	80mg

AND

☐ ondansetron _____ mg (0.15 mg/kg/dose or 5 mg/m^2/dose, *maximum dose 8 mg*) IV/PO every 8 hours. Start 30 minutes prior to chemotherapy if using IV antiemetic or 60 minutes prior to chemotherapy if using PO antiemetic.

OR

Only for patients uncontrolled on ondansetron **or** stabilized on granisetron:

☐ granisetron _____ mg (0.02 to 0.04 mg/kg/dose) IV/PO every 12 hours. Start 30 minutes prior to chemotherapy if using IV antiemetic or 60 minutes prior to chemotherapy if using PO antiemetic.

AND

☐ dexamethasone _____mg (2.5 mg/m^2/dose) IV/PO every 12 hours. Start 30 minutes prior to chemotherapy if using IV antiemetic or 60 minutes prior to chemotherapy if using PO antiemetic.

OR

☐ dexamethasone _____mg IV/PO every _____hours. Start 30 minutes prior to chemotherapy if using IV antiemetic or 60 minutes prior to chemotherapy if using PO antiemetic. (*Dose and/or frequency may be increased on a case-by-case basis to a maximum of 5 mg/m^2/dose PO/IV every 6 hours or a daily maximum of 16 mg. Doses up to 12 mg/day of dexamethasone do not require adjustment when given concurrently with aprepitant.)*

For Breakthrough Nausea and Vomiting

☐ OLANZapine _____mg (0.1 mg/kg/dose; *round to the nearest 1.25 mg, maximum dose 10 mg*) PO daily for breakthrough nausea/ vomiting NOTE: 0.03-0.3 mg/kg/dose have been used

☐ LORazepam _____ mg (0.025 to 0.08 mg/kg/dose) IV/PO/SL every _____ (*choose one: 6 hours, 8 hours, 6 hours PRN, 8 hours PRN*) for breakthrough nausea/ vomiting

☐ nabilone _____ mg *(Use table below to guide ordering)* PO _____ (*choose one: BID, TID, BID PRN, TID PRN*)

Body Weight (kg)	Nabilone Dose
Less than 18 kg	0.5 mg PO BID
18 kg to 30 kg	1 mg PO BID
Greater than 30 kg	1 mg PO TID

☐ metoclopramide _____ mg (1 mg/kg/dose) IV/PO every _____(*choose one: 6 hours, 8 hours, 6 hours PRN, 8 hours PRN*). (*Usual adult dose is 10 mg);* to be given concurrently with diphenhydrAMINE to prevent extrapyramidal side effects.

☐ diphenhydrAMINE _____ mg (1 mg/kg/dose) IV/PO every _____(*choose one: 6 hours, 8 hours 6 hours PRN, 8 hours PRN*); to be given concurrently with **regularly scheduled** metoclopramide to prevent extrapyramidal side effects.

☐ Other:_____

For Anticipatory Nausea and Vomiting

☐ LORazepam _____ mg (0.04 to 0.08 mg/kg/dose; *maximum dose 2 mg*) PO/SL ONCE at bedtime before day 1 of chemotherapy cycle **and then** may repeat dose 12 hours later on the morning of chemotherapy.

On discharge:

Patients administered chemotherapy that may cause delayed nausea and vomiting (CISplatin, cyclophosphamide, ifosfamide, anthracyclines, CARBOplatin), may experience CINV up to 7 days after the last dose of chemotherapy.

☑ Discharge Instructions: Ensure discharge prescriptions include appropriate antiemetics for at least 24-48 hours after last dose of chemotherapy.

☑ Discharge Instructions: Ensure Pediatric Nausea Assessment Tool (PeNAT) is provided to families with appropriate contact information for uncontrolled chemotherapy induced nausea and vomiting.

Reminder

- Emetogenicity of Antineoplastic Medications in Pediatric Cancer Patients Given as Single Agents[2,19]
    - Trigger for Reminder:
        - When a medication is ordered from Column A the reminder associated in Column B should be displayed for the prescriber.

Table 8. Reminder for emetogenicity of antineoplastic medications in pediatric cancer patients

Column A: Medication ordered	Column B: Reminder to display to clinician
altretamine[a] *CARBOplatin[a] carmustine greater than 250 mg/m^2[a] *CISplatin[a] *cyclophosphamide greater than or equal to 1 g/m^2[a] *cytarabine 3 g/m2/dose dacarbazine[a] *dactinomycin hexamethylmelamine (oral)[b] mechlorethamine[a] *methotrexate greater than or equal to 12 g/m^2[a] procarbazine (oral)[a] streptozocin[a] *thiotepa greater than or equal to 300 mg/m^2	High Emetogenicity Risk: Consider ondansetron/granisetron, dexamethasone, aprepitant
aldesleukin greater than 12 to 15 million units/m^2[a] alemtuzumab[b,c] amifostine greater than 300 mg/m^2[a] arsenic trioxide[a] azaCITIDine [a,] bendamustine[a] bosutinib (oral)[b] busulfan[a] *carmustine less than or equal to 250 mg/m^2[a] ceritinib(oral)[b] *clofarabine[a] crizotinib(oral)[b] *cyclophosphamide less than 1 g/m^2[a] cyclophosphamide (oral)[a] cytarabine greater than 200 mg/m^2 to less than 3 g/m^2[a] *DAUNOrubicin[a,] *DOXorubicin[a,]	Moderate Emetogenicity Risk: Consider ondansetron/graniestron, dexamethasone

epirubicin[a] etoposide (oral)[a] IDArubicin[a.] ifosfamide[a,] imatinib (oral)[a,] *intrathecal therapy (methotrexate, hydrocortisone & cytarabine)[a] irinotecan[a] lomustine[a] melphalan greater than 50 mg/m^{2}[a] methotrexate greater than or equal to 250 mg to less than 12 g/m^{2}[a] oxaliplatin greater than 75 mg/m^{2}[a] (dose not included)[b] romidepsin[b] temozolomide (oral)[a] trabectedin[b] vinorelbine (oral)[a,]	
afatinib(oral)[b] aflibercept[b] amifostine less than or equal to 300 mg/m^{2}[a] amsacrine[a] axatinib(oral)[b] belinostat[b] bexarotene[a] blinatumomab[b] bortezomib[b,c] brentuximab[b] *busulfan (oral)[a] cabazitaxel[b] capecitabine[a] capecitabine(oral)[b] carfilzomib[b] catumaxumab[b] cetuximab[b,c] cytarabine less than or equal to 200 mg/m^{2}[a] dabrafenib (oral)[b] dasatinib (oral)[b,c] DOCEtaxel[a] DOXOrubicin (liposomal)[a] eribulin[b] etoposide[a] etoposide (oral)[b] everolimus (oral)[b] fludarabine (oral)[a] 5-fluorouracil[a] gemcitabine[a] ibrutinib (oral)[b] idelalisib (oral)[b] ipilimumab[b]	Low Emetogenicity Risk: Consider ondansetron/granisetron

ixabepilone[a]
lapatinib (oral)[b]
lenalidomide(oral)[b]
methotrexate greater than 50 mg/m^2 to less than 250 mg/m^2[a]
mitomycin[a]
mitoXANTRONE[a,]
nab-PACLitaxel[b]
nilotinib[a]
nilotinib(oral)[b]
olaparib(oral)[b]
PACLitaxel[a]
PACLitaxel-albumin[a]
panitumumab[b,c]
pazopanib(oral)[b]
pegylated liposomal DOXOrubicin[b]
pemetrexed[a]
pertuzumab[b]
ponatinib(oral)[b]
regorafenib(oral)[b]
SUNitinib(oral)[b]
temsirolimus[b,c]
teniposide[a]
tegafur uracil(oral)[b]
thalidomide(oral)[b]
thiotepa less than 300 mg/m2[a]
topotecan[a]
trastuzumab-emtansine[b]
vinflunine[b]
vandetanib(oral)[b]
vorinostat[a]
vorinostat (oral)[b]

Note:
All agents given intravenously (IV) unless stated otherwise.
Classified emetic potential of oral agents based upon a full course of therapy and not a single dose.[b]

* Pediatric evidence available

[a] Dupuis L, Boodhan S, Sung, L et al. *Guideline For the Classification of Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Cancer Patients* Pediatr Blood Cancer 2011, 57:191-198.

[b] Rolia F, Molassiotis A, Herrstedt J et al. *2016 MASCC and ESMO Guideline Update For the Prevention of Chemotherapy- and Radiotherapy-Induced Nausea and Vomiting and of Nausea and Vomiting in Advanced Cancer Patients.* Annals of Oncology 2016; 27 (Supplement 5): v119-133

[c]Emetogenicity rating based on MASCC Guideline[b] as rating was higher than Pediatric Oncology Group of Ontario (POGO) Guideline[a]

Analytics

Baseline Analytics – Outcome Measure#1

Name of Measure	Number of times order set "Pediatric Chemotherapy Induced Nausea and Vomiting" is used
Definition	For all pediatric patients receiving High, Moderate or Low Emetogenic Chemotherapy, number of times "Pediatric Chemotherapy Induced Nausea and Vomiting" order set is used. Overall, by region, by sites, and by units
Rationale	Intended to measure if the order set cited in the knowledge topic is being used for patient's prescribed high, moderate or low emetogenic chemotherapy. May indicate areas with adoption issues or gaps in topic

Baseline Analytics – Outcome Measure#2

Name of Measure	Compliance to clinical standards of order set "Pediatric Chemotherapy Induced Nausea and Vomiting"
Definition	What % of time were the antiemetics recommended for HEC, MEC and LEC ordered within the order set "Pediatric Chemotherapy Induced Nausea and Vomiting" followed for patients receiving chemotherapy for malignant indications?
Rationale	Intended to show compliance with clinical standards, site capacity, rural considerations, roll out of provincial CIS
Notes for Interpretation	Health record must have coding for disease/condition, site capacity, rural considerations, roll out of provincial CIS

Keywords

- antiemetic
- cancer
- oncology
- chemotherapy
- nausea
- vomiting
- emesis

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Appendix A- List of Antineoplastic Agent and By Emetic Risk

Table 9. Classification of the Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Cancer Patients Given as Single Agents[2,19]

High Level of Emetic Risk (greater than 90% frequency of emesis in absence of prophylaxis)	
altretamine[a]	*dactinomycin[a]
*CARBOplatin[a]	hexamethylmelamine (oral)[b]
Carmustine greater than 250 mg/m^2[a]	mechlorethamine[a]
*CISplatin[a.]	*methotrexate greater than or equal to 12 g/m^2 [a]
*Cyclophosphamide greater than or equal to 1 g/m^2[a]	procarbazine (oral)[a]
*cytarabine 3 g/m2/dose[a]	streptozocin[a]*
dacarbazine[a]	thiotepa greater than or equal to 300 mg/m^2 [a]
Moderate Level of Emetic Risk (30-90% frequency of emesis in absence of prophylaxis)	
aldesleukin greater than 12 to 15 million units/m^2[a]	epirubicin[a]
alemtuzumab[b, c]	etoposide (oral)[a]
amifostine greater than 300 mg/m^2[a]	IDArubicin[a]
arsenic trioxide[a]	ifosfamide[a]
azaCITIDine[a]	imatinib (oral)[a]
bendamustine[a]	*Intrathecal therapy (methotrexate, hydrocortisone & cytarabine)[a]
bosutinib (oral)[b]	irinotecan[a]
busulfan[a]	lomustine[a]
*carmustine less than or equal to 250 mg/m^2[a]	melphalan greater than 50 mg/m^2[a]
ceritinib(oral)[b]	methotrexate greater than or equal to 250 mg to less than 12 g/m^2[a]
*clofarabine[a]	oxaliplatin greater than 75 mg/m^2[a]
crizotinib(oral)[b]	romidepsin[b]
*cyclophosphamide less than 1 g/m^2[a]	temozolomide (oral)[a]
cyclophosphamide (oral)[a]	trabectedin[b]
cytarabine greater than 200 mg/m^2 to less than 3 g/m^2[a]	vinorelbine (oral)[a]
*DAUNOrubicin[a]	
*DOXorubicin[a]	
Low Level of Emetic Risk (10-less than30% frequency of emesis in absence of prophylaxis)	
afatinib(oral)[b]	ixabepilone[a]
aflibercept[b]	lapatinib (oral)[b]
amifostine less than or equal to 300 mg/m^2[a]	lenalidomide(oral)[b]
amsacrine[a]	methotrexate greater than 50 mg/m^2 to less than 250 mg/m^2[a]
axatinib(oral)[b]	mitomycin[a]
belinostat[b]	mitoXANTRONE[a]
bexarotene[a]	nab-PAClitaxel[b]
blinatumomab[b]	nilotinib[a]
bortezomib[b,c]	nilotinib(oral)[b]
brentuximab[b]	olaparib(oral)[b]
*busulfan (oral)[a]	PAClitaxel[a]
cabazitaxel[b]	PAClitaxel-albumin[a]
capecitabine[a]	panitumumab[b,c]
capecitabine(oral)[b]	

carfilzomib[b]	pazopanib(oral)[b]
catumaxumab[b]	pegylated liposomal DOXOrubicin[b]
cetuximab[b,c]	pemetrexed[a]
cytarabine less than or equal to 200 mg/m2[a]	pertuzumab[b]
dabrafenib (oral)[b]	ponatinib(oral)[b]
dasatinib (oral)[b,c]	regorafenib(oral)[b]
DOCEtaxel[a]	sunitinib(oral)[b]
DOXOrubicin (liposomal)[a]	temsirolimus[b,c]
eribulin[b]	teniposide[a]
etoposide[a]	tegafur uracil(oral)[b]
etoposide (oral)[b]	thalidomide(oral)[b]
everolimus (oral)[b]	thiotepa less than 300 mg/m2[a]
fludarabine (oral)[a]	topotecan[a]
5-fluorouracil[a]	trastuzumab-emtansine[b]
gemcitabine[a]	vinflunine[b]
ibrutinib (oral)[b]	vandetanib(oral)[b]
idelalisib (oral)[b]	vorinostat[a]
ipilimumab[b]	vorinostat (oral)[b]

Minimal (less than10% frequency of emesis in absence of prophylaxis)	
alpha interferon[a]	nivolumab[b]
asparaginase (IM or IV)[a]	ofatumumab[b]
bevacizumab[a]	pembrolizumab[b]
bleomycin[a]	pentostatin[a]
chlorambucil (oral)[a]	pixantrone[b]
cladribine (2-chlorodeoxyadenosine)[a]	pomalidomide (oral)[b]
decitabine[a]	pralatrexate[b]
denileukin diftitox[a]	riTUXimab[a]
dexrazoxane[a]	ruxolitinib (oral)[b]
erlotinib[a]	SORAfenib[a]
erlotinib (oral)[b]	SORAfenib (oral)[b]
fludarabine[a]	SUNItinib[a]
gefitinib[a]	thalidomide[a]
gefitinib (oral)[b]	thioguanine (oral)[a]
gemtuzumab ozogamicin[a]	6-thioguanine (oral)[b]
hydroxyurea (oral)[a]	trastuzumab[a]
lapatinib[a]	valrubicin[a]
lenalidomide[a]	vemurafenib (oral)[b]
l-phenylalanine mustard (oral)[b]	vinBLAStine[a]
melphalan (oral low-dose)[a]	vinCRIStine[a]
mercaptopurine (oral)[a]	vindesine[a]
methotrexate less than or equal to 50 mg/m2[a]	vinorelbine[a]
methotrexate (oral)[b]	vismodegib (oral)[b]
nelarabine[a]	

Note:
All agents given intravenously (IV) unless stated otherwise.
Classified emetic potential of oral agents based upon a full course of therapy and not a single dose.[b]

* Pediatric evidence available

[a] Dupuis L, Boodhan S, Sung, L et al. Guideline For the Classification of Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Cancer Patients

[b] Rolia F, Molassiotis A, Herrstedt J et al. *2016 MASCC and ESMO Guideline Update For the Prevention of Chemotherapy- and Radiotherapy-Induced Nausea and Vomiting and of Nausea and Vomiting in Advanced Cancer Patients.* Annals of Oncology 2016; 27 (Supplement 5): v119-133
[c]Emetogenicity rating based on MASCC Guideline[b] as rating was higher than Pediatric Oncology Group of Ontario (POGO) Guideline[a]

Table 10: Classification of the Acute Emetogenic Potential of Specific Antineoplastic Medication in Pediatric Cancer Patients Given in Combination[2]

High Level of Emetic Risk (greater than 90% frequency of emesis in absence of prophylaxis)
cyclophosphamide + anthracycline
*cyclophosphamide +
DOXOrubicin*cyclophosphamide + epirubicin
*cyclophosphamide + etoposide
*cytarabine 150-200 mg/m^2 + DAUNOrubicin
*cytarabine 300 mg/m^2 + etoposide
*cytarabine 300 mg/m^2 + teniposide
*DOXOrubicin + ifosfamide
DOXOrubicin + methotrexate 5 g/m^2
*etoposide + ifosfamide

Note: All agents given intravenously (IV) unless stated otherwise.
* Pediatric evidence available
Source: Dupuis L, Boodhan S, Sung, L et al. Guideline For the Classification of Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Cancer Patients

Appendix B- Alphabetical List of Antineoplastic Agent and Emetic Risk[2,19]

Table 11: Alphabetical List of Antineoplastic Agent and Emetic Risk	
5-fluorouracil[a]	Low
6-thioguanine (oral) [a]	Minimal
afatinib(oral)[b]	Low
aflibercept[b]	Low
aldesleukin greater than 12 to 15 million units/m^2[a]	Moderate
alemtuzumab[b,c]	Moderate
alpha interferon[a]	Minimal
altretamine[a]	High
amifostine greater than 300 mg/m^2[a]	Moderate
amifostine less than or equal to 300 mg/m^2[a]	Low
amsacrine[a]	Low
anthracycline + cyclophosphamide[a] *cyclophosphamide + DOXOrubicin[a] *cyclophosphamide + epirubicin[a]	High
arsenic trioxide[a]	Moderate
asparaginase (IM or IV) [a]	Minimal
axatinib(oral)[b]	Low
azacitidine[a]	Moderate
belinostat[b]	Low
bendamustine[a]	Moderate
bevacizumab[a]	Minimal
bexarotene[a]	Low
bleomycin[a]	Minimal
blinatumomab[b]	Low
bortezomib[b,c]	Low
bosutinib (oral)[b]	Moderate
brentuximab[b]	Low
busulfan[a]	Moderate
busulfan (oral) [a]	Low
cabazitaxel[b]	Low
capecitabine[a]	Low
carfilzomib[b]	Low
capecitabine(oral)[b]	Low

CARBOplatin*[a]	High
carmustine greater than 250 mg/m^{2}[a]	High
carmustine less than or equal to 250 mg/m^{2}*[a]	Moderate
catumaxumab[b]	Low
ceritinib(oral)[b]	Moderate
cetuximab[b,c]	Low
chlorambucil (oral) [a]	Minimal
CISplatin*[a]	High
cladribine (2-chlorodeoxyadenosine)[a]	Minimal
clofarabine*[a]	Moderate
crizotinib(oral)[b]	Crizotinib(oral)[b]
cyclophosphamide (oral) [a]	Moderate
cyclophosphamide less than 1 g/m^{2}*[a]	Moderate
cyclophosphamide greater than or equal to1 g/m^{2}*[a]	High
cyclophosphamide + anthracycline[a] *cyclophosphamide + DOXOrubicin[a] *cyclophosphamide + epirubicin[a]	High
cyclophosphamide + etoposide	High
cytarabine greater than 200 mg to less than 3 g/m^{2}[a]	Moderate
cytarabine less than or equal to 200 mg/m^{2}[a]	Low
cytarabine 3 g/m2/dose*[a]	High
cytarabine 150-200 mg/m^{2} + DAUNOrubicin*[a]	High
cytarabine 300 mg/m^{2} + etoposide*[a]	High
cytarabine 300 mg/m^{2} + teniposide*[a]	High
cytarabine, methotrexate + hydrocortisone: intrathecal therapy*[a]	Moderate
dabrafenib (oral)[b]	Low
dacarbazine[a]	High
dactinomycin*[a]	High
DAUNOrubicin*[a]	Moderate
DAUNOrubicin + cytarabine 150-200 mg/m^{2}*[a]	High
dasatinib (oral)[b,c]	Low
decitabine[a]	Minimal
denileukin diftitox[a]	Minimal
dexrazoxane[a]	Minimal
DOCEtaxel[a]	Low
DOXOrubicin (liposomal) [a]	Low
DOXOrubicin*[a]	Moderate

DOXOrubicin + cyclophosphamide*[a]	High
DOXOrubicin + ifosfamide*[a]	High
DOXOrubicin + methotrexate 5 g/m[a2]	High
epirubicin[a]	Moderate
epirubicin + cyclophosphamide*[a]	High
eribulin[b]	Low
erlotinib[a]	Minimal
erlotinib (oral)[b]	Minimal
etoposide[a]	Low
etoposide (oral)[a]	Moderate
etoposide + cyclophosphamide*[a]	High
etoposide + cytarabine 300 mg/m^2*[a]	High
etoposide + ifosfamide*[a]	High
everolimus (oral)[b]	Low
eludarabine[a]	Minimal
eludarabine (oral) [a]	Low
gefitinib[a]	Minimal
gefitinib (oral)[b]	Minimal
gemcitabine[a]	Low
gemtuzumab ozogamicin[a]	Minimal
hexamethylmelamine (oral)[b]	High
hydrocortisone, cytarabine + methotrexate: intrathecal therapy*[a]	Moderate
hydroxyurea (oral) [a]	Minimal
ibrutinib (oral)[b]	Low
IDArubicin[a]	Moderate
idelalisib (oral)[b]	Low
ifosfamide[a]	Moderate
ifosfamide + doxorubicin*[a]	High
ifosfamide + etoposide*[a]	High
imatinib (oral) [a]	Moderate
intrathecal therapy (methotrexate, hydrocortisone & cytarabine)* [a]	Moderate
Ipilimumab[b]	Low
irinotecan[a]	Moderate
ixabepilone[a]	Low
lapatinib[a]	Minimal
lapatinib (oral)[b]	Low

lenalidomide[a]	Minimal
lenalidomide(oral)[b]	Low
lomustine[a]	Moderate
l-phenylalanine mustard (oral)[b]	Minimal
mechlorethamine[a]	High
melphalan (oral low-dose) [a]	Minimal
melphalan greater than 50 mg/m^2[a]	Moderate
mercaptopurine (oral) [a]	Minimal
methotrexate greater than 50 mg/m^2 to less than 250 mg/m^2[a]	Low
methotrexate less than or equal to 50 mg/m^2[a]	Minimal
methotrexate greater than or equal to 12 g/m^2*[a]	High
methotrexate greater than or equal to 250 mg/m^2 to less than 12 g/m^2[a]	Moderate
methotrexate 5 g/m^2 + Doxorubicin[a]	High
methotrexate, hydrocortisone + cytarabine: intrathecal therapy*[a]	Moderate
mitomycin[a]	Low
mitoXANTRONE[a]	Low
nab-paclitaxel[b]	Low
nelarabine[a]	Minimal
Nilotinib[a]	Low
nilotinib(oral)[b]	Low
olaparib(oral)[b]	Low
oxaliplatin greater than 75 mg/m^2[a]	Moderate
PAClitaxel[a]	Low
PAClitaxel-albumin[a]	Low
panitumumab[b,c]	Low
pazopanib(oral)[b]	Low
pegylated liposomal DOXOrubicin[b]	Low
pemetrexed[a]	Low
pentostatin[a]	Minimal
pertuzumab[b]	Low
ponatinib(oral)[b]	Low
procarbazine (oral) [a]	High
regorafenib(oral)[b]	Low
riTUXimab[a]	Minimal
romidepsin[b]	Moderate

SORAfenib[a]	Minimal
streptozocin[a]	High
SUNitinib[a]	Minimal
SUNitinib(oral)[b]	Low
tegafur uracil(oral)[b]	Low
temozolomide (oral) [a]	Moderate
temsirolimus[b,c]	Low
teniposide[a]	Low
teniposide + cytarabine 300 mg/m^{2}*[a]	High
thalidomide[a]	Minimal
thalidomide(oral)[b]	Low
thioguanine (oral)[a]	Minimal
thiotepa less than 300 mg/m^{2}[a]	Low
thiotepa greater than or equal to 300 mg/m^{2}*[a]	High
topotecan[a]	Low
trabectedin[b]	Moderate
trastuzumab[a]	Minimal
trastuzumab-emtansine[b]	Low
valrubicin[a]	Minimal
vandetanib(oral)[b]	Minimal
vinBLAStine[a]	Minimal
vinCRIStine[a]	Minimal
vindesine[a]	Minimal
vinflunine[b]	Low
vinorelbine[a]	Minimal
vinorelbine (oral) [a]	Moderate
vismodegib (oral)[b]	Minimal
vorinostat[a]	Low
vorinostat (oral)[b]	Low

High = High Level of Emetic Risk (greater than 90% frequency of emesis in absence of prophylaxis)
Moderate = Moderate Level of Emetic Risk (30-90% frequency of emesis in absence of prophylaxis)
Low = Low Level of Emetic Risk (10-less than30% frequency of emesis in absence of prophylaxis)
Minimal = Minimal Level of Emetic Risk (less than10% frequency of emesis in absence of prophylaxis)
Note: All agents given intravenously (IV) unless stated otherwise.
Classified emetic potential of oral agents based upon a full course of therapy and not a single dose.[b]

* Pediatric evidence available

[a] Dupuis L, Boodhan S, Sung, L et al. Guideline For the Classification of Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Cancer Patients

[b] Rolia F, Molassiotis A, Herrstedt J et al. *2016 MASCC and ESMO Guideline Update For the Prevention of Chemotherapy- and Radiotherapy-Induced Nausea and Vomiting and of Nausea and Vomiting in Advanced Cancer Patients.* Annals of Oncology 2016; 27 (Supplement 5): v119-133

[c]Emetogenicity rating based on MASCC Guideline[b] as rating was higher than Pediatric Oncology Group of Ontario (POGO) Guideline[a]

Appendix C – Pediatric Nausea Assessment Tool (PeNAT)[18]

- For patients aged 4-8 years
- For patients older than 8 years

Alberta Health Services

Addressograph Label

Chemotherapy Start Date:
_____

Patient Diary

For your child aged 4–8 years

Each time your child is receiving chemotherapy on the unit, we will give you a new diary sheet. Please return it at your next clinic visit after completing chemotherapy to review with the team.
What is your family term for vomiting? _____.

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 _____.

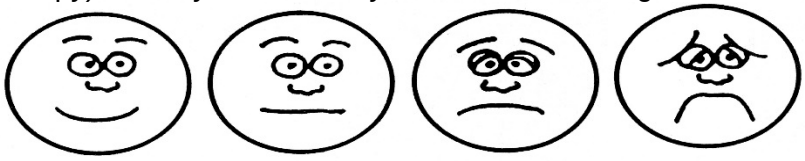
If no, have you ever felt like you were going to throw up (use family term) but didn't?
If yes, how did your tummy feel then? _____. We call that feeling nausea or being nauseous. In your family you call that feeling _____.
Some children who get chemo feel nauseous (use family term) and some don't. Right 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?

Use the faces to describe how bad your child's nausea (or family term) is. Write down the number below the face that describes how they feel. Write down the time that they rated their nausea in the box. Rate their nausea two separate times each day (before and after chemotherapy) and anytime that they need a 'breakthrough' medication.



1 2 3 4

Nausea

	Time 1	Rating	Time 2	Rating	Other time(s)	Rating
Prior to						
Day 1						
Day 2						
Day 3						
Day 4						
Day 5						
After last chemo						

Alberta Health Services

Addressograph Label

Chemotherapy Start Date: _____

Patient Diary

To the child older than 8 years:

Each time your child is receiving chemotherapy on the unit, we will give you a new diary sheet. Please return it at your next clinic visit after completing chemotherapy to review with the team.

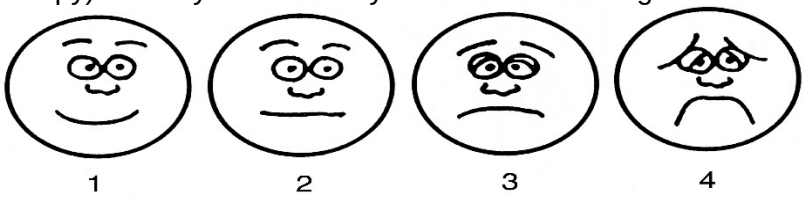
Have you ever thrown up (use family term) before?
If yes, how did your tummy/stomach feel just before you threw up (use family term)? _____.
We call that feeling nausea or being nauseous. In your family you call that feeling _____.

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?

Use the faces to describe how bad your child's nausea (or family term) is. Write down the number below the face that describes how they feel. Write down the time that they rated their nausea in the box. Rate their nausea two separate times each day (before and after chemotherapy) and anytime that they need a 'breakthrough' medication.



Nausea

	Time 1	Rating	Time 2	Rating	Other time(s)	Rating
Prior to chemotherapy						
Day 1						
Day 2						
Day 3						
Day 4						
Day 5						
After last chemo						

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