Guideline for Classification of the Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Cancer Patients

POGO Antineoplastic – Induced Nausea and Vomiting Guideline Development Panel:

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The POGO Emetogenicity Classification Guidelines were developed by health care professionals using evidence-based or best practice references available at the time of their creation. Format and content of the guidelines will change as they are reviewed and revised on a periodic basis. Care has been taken to ensure accuracy of the information. However, every health care professional using these guidelines is responsible for providing care according to their best professional judgement and the policies and standards of care in place at their own institution.

OVERVIEW OF MATERIAL

**Guideline Release Date:** August 11, 2010

**Status:** Adapted, revised and updated

**Sources:**
- Print copies available through POGO
- Electronic sources available through [www.pogo.ca](http://www.pogo.ca)

**Adapters:** POGO Antineoplastic-induced Nausea and Vomiting Guideline Development Panel
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**SUMMARY**

**RECOMMENDATIONS**

On the basis of the identified evidence and the expert consensus of the POGO Antineoplastic–induced Nausea and Vomiting Guideline Development Group, the following classification of the acute emetogenic potential of antineoplastic medication in pediatric cancer patients is recommended:

**Recommendation:** The single antineoplastic agents provided in Table 1 have high, moderate, low or minimal emetogenic potential in children.

| High Level of Emetic Risk (> 90% frequency of emesis in absence of prophylaxis) |
| Altretamine |
| *Carboplatin |
| Carmustine > 250 mg/m² |
| *Cisplatin |
| *Cyclophosphamide ≥ 1 g/m² |
| *Cytarabine 3 g/m²/dose |
| Dacarbazine |
| *Dactinomycin |
| Mechlorethamine |
| *Methotrexate ≥ 12 g/m² |
| Procarbazine (oral) |
| Streptozocin |
| *Thiotepa ≥ 300 mg/m² |

| Moderate Level of Emetic Risk (30-90% frequency of emesis in absence of prophylaxis) |
| Aldesleukin > 12 to 15 million units/m² |
| Amifostine > 300 mg/m² |
| Arsenic trioxide |
| Azacitidine |
| Bendamustine |
| Busulfan |
| *Carmustine ≤ 250 mg/m² |
| *Clofarabine |
| *Cyclophosphamide < 1 g/m² |
| Cyclophosphamide (oral) |
| Cytarabine > 200 mg/m² to < 3 g/m² |
| *Daunorubicin |
| *Doxorubicin |
| Epirubicin |
| Etoposide (oral) |
| Idarubicin |
| Ifosfamide |
| Imatinib (oral) |
| *Intrathecal therapy (methotrexate, hydrocortisone & cytarabine) |
| Irinotecan |
| Lomustine |
| Melphalan > 50 mg/m² |
| Methotrexate ≥ 250 mg to < 12 g/m² |
| Oxaliplatin > 75 mg/m² |
| Temozolomide (oral) |
| Vinorelbine (oral) |

| Low Level of Emetic Risk (10-30% frequency of emesis in absence of prophylaxis) |
| Amifostine ≤ 300 mg/m² |
| Amsacrine |
| Bexarotene |
| *Busulfan (oral) |
| Capecitabine |
| Cytarabine ≤ 200 mg/m² |
| Docetaxel |
| Doxorubicin (liposomal) |
| Etoposide |
| Fludarabine (oral) |
| 5-Fluorouracil |
| Gemcitabine |
| Ixabepilone |
| Methotrexate > 50 mg/m² to < 250 mg/m² |
| Mitomycin |
| Mitoxantrone |
| Nilotinib |
| Paclitaxel |
| Paclitaxel-albumin |
| Pemetrexed |
| Teniposide |
| Thiotepa < 300 mg/m² |
| Topotecan |
| Vorinostat |

* Pediatric evidence available

**Note:** All agents given intravenously (IV) unless stated otherwise.
Table 1: Classification of the Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Cancer Patients Given as Single Agents (continued)

<table>
<thead>
<tr>
<th>Minimal (&lt;10% frequency of emesis in absence of prophylaxis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alemtuzumab</td>
</tr>
<tr>
<td>Alpha interferon</td>
</tr>
<tr>
<td>Asparaginase (IM or IV)</td>
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<tr>
<td>Bevacizumab</td>
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<tr>
<td>Bleomycin</td>
</tr>
<tr>
<td>Bortezomib</td>
</tr>
<tr>
<td>Cetuximab</td>
</tr>
<tr>
<td>Chlorambucil (oral)</td>
</tr>
<tr>
<td>Cladribine (2-chlorodeoxyadenosine)</td>
</tr>
<tr>
<td>Decitabine</td>
</tr>
<tr>
<td>Denileukin diftitox</td>
</tr>
<tr>
<td>Dasatinib</td>
</tr>
<tr>
<td>Dexamethasone</td>
</tr>
<tr>
<td>Fludarabine</td>
</tr>
<tr>
<td>Gefitinib</td>
</tr>
<tr>
<td>Gemtuzumab ozogamicin</td>
</tr>
<tr>
<td>Hydroxyurea (oral)</td>
</tr>
<tr>
<td>Lapatinib</td>
</tr>
<tr>
<td>Lenalidomide</td>
</tr>
<tr>
<td>Melphalan (oral low-dose)</td>
</tr>
<tr>
<td>Mercaptopurine (oral)</td>
</tr>
<tr>
<td>Methotrexate ≤ 50 mg/m²</td>
</tr>
<tr>
<td>Nelarabine</td>
</tr>
<tr>
<td>Panitumumab</td>
</tr>
<tr>
<td>Pentostatin</td>
</tr>
<tr>
<td>Rituximab</td>
</tr>
<tr>
<td>Sorafenib</td>
</tr>
<tr>
<td>Sunitinib</td>
</tr>
<tr>
<td>Temsirolium</td>
</tr>
<tr>
<td>Thalidomide</td>
</tr>
<tr>
<td>Thioquanine (oral)</td>
</tr>
<tr>
<td>Trastuzumab</td>
</tr>
<tr>
<td>Valrubicin</td>
</tr>
<tr>
<td>Vinblastine</td>
</tr>
<tr>
<td>Vincristine</td>
</tr>
<tr>
<td>Vindesine</td>
</tr>
<tr>
<td>Vinorelbine</td>
</tr>
</tbody>
</table>

* Pediatric evidence available

Note: All agents given intravenously (IV) unless stated otherwise.

Recommendation: With the exceptions noted in Table 2 below, the emetogenicity of multiple agent antineoplastic therapy given to children is classified based on the emetogenic potential of the most highly emetogenic agent in the combination to be given.

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

<table>
<thead>
<tr>
<th>High Level of Emetic Risk (&gt; 90% frequency of emesis in absence of prophylaxis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide + anthracycline</td>
</tr>
<tr>
<td>*Cyclophosphamide + doxorubicin</td>
</tr>
<tr>
<td>*Cyclophosphamide + epirubicin</td>
</tr>
<tr>
<td>*Cyclophosphamide + etoposide</td>
</tr>
<tr>
<td>*Cytarabine 150-200 mg/m² + daunorubicin</td>
</tr>
<tr>
<td>*Cytarabine 300 mg/m² + etoposide</td>
</tr>
<tr>
<td>*Cytarabine 300 mg/m² + teniposide</td>
</tr>
<tr>
<td>*Doxorubicin + ifosfamide</td>
</tr>
<tr>
<td>Doxorubicin + methotrexate 5 g/m²</td>
</tr>
<tr>
<td>*Etoposide + ifosfamide</td>
</tr>
</tbody>
</table>

* Pediatric evidence available

Note: All agents given intravenously (IV) unless stated otherwise.

Recommendation: The emetogenicity of multiple day antineoplastic therapy is classified in children based on the emetogenic potential of the most highly emetogenic agent on each day of therapy.
GLOSSARY

Emetogenicity: the propensity of an agent to cause nausea, vomiting or retching.

High emetic potential: greater than 90% frequency of emesis in the absence of effective prophylaxis.

Moderate emetic potential: 30 to 90% frequency of emesis in the absence of effective prophylaxis.

Low emetic potential: 10 to less than 30% frequency of emesis in the absence of effective prophylaxis.

Minimal emetic potential: less than 10% frequency of emesis in the absence of effective prophylaxis.

Acute phase antineoplastic-induced nausea and vomiting: Nausea, vomiting, and/or retching that occurs within 24 hours of administration of an antineoplastic therapy.

Delayed phase antineoplastic-induced nausea and vomiting: Nausea, vomiting, and/or retching that occurs more than 24 hours after and usually within 7 days of administration of an antineoplastic therapy.
INTRODUCTION

Antineoplastic-induced nausea and vomiting (AINV) reduces quality of life for all patients receiving antineoplastic therapy, including children. AINV may actually be more prevalent and have a greater impact upon children than adults, since children usually receive more dose-intensive treatment over longer duration compared with adults. Nausea is identified by parents of children receiving active antineoplastic therapy in Ontario as the fourth most prevalent and bothersome treatment-related symptom seen in their children. Available evidence indicates that several commonly administered chemotherapy regimens produce significant AINV even with administration of the best available antiemetic strategies. Despite the importance of AINV control in children, pediatric antiemetic drug development has lagged behind that for adults. For instance, the first agent of the latest class of antiemetic agents (NK-1 antagonists) was licensed for use in adults in the United States in 2006 and in Canada in 2007 but safe and effective aprepitant dosing has yet to be established in children.

Current approaches to the selection of appropriate and effective measures to prevent AINV are founded on an accurate description of the potential of antineoplastic therapies to cause nausea and vomiting. However, all recently published guidelines for the management of AINV are for adults based upon emetogenic potential of chemotherapy regimens employed in adult oncology.

SCOPE AND PURPOSE

The purpose of this guideline is to provide physicians, nurses, pharmacists and other health care providers who care for children aged 1 month to 18 years who are receiving antineoplastic medication with an approach to assess the emetogenic potential of antineoplastic regimens. Assessment of the emetogenic potential of antineoplastic therapy is the first step in the decision of whether or not, and to what extent, to provide antiemetic prophylaxis. The scope of this guideline is limited to the assessment of antineoplastic therapy emetogenicity in the acute phase (within 24 hours of administration of an antineoplastic agent). Its scope does not include anticipatory, breakthrough or delayed phase AINV, or nausea and vomiting that is related to radiation therapy, disease, coincident conditions or end-of-life care. In addition, this guideline is most applicable to children who are naïve to antineoplastic therapy and who are about to receive their first course of antineoplastic therapy. In the case of children who have received antineoplastic medication in the past, estimation of the emetogenic potential of the antineoplastic regimen to be given incorporates both the recommendations of this guideline and an assessment of the child’s previous experience with AINV.

This guideline represents the first of a series of guidelines to address the need for, and the selection of, antiemetic prophylaxis and intervention in children with cancer receiving antineoplastic therapy. These guidelines will lead to improvements in the supportive care of children with cancer by offering a standardized, evidence-based approach to the prophylaxis of AINV, optimization of AINV control and provision of cost-effective antiemetic prophylaxis.

The objectives of this guideline are:

1. To facilitate the assessment of the emetogenic potential of antineoplastic medication in the acute phase and the need for antiemetic prophylaxis in children with cancer;

2. To incorporate an appreciation for the impact of multiple agent and multiple day antineoplastic therapy, including conditioning for hematopoietic stem cell transplant (HSCT), into the assessment of the emetogenicity of antineoplastic therapies in children;

3. To reduce the impact of inconsistent antiemetic prophylaxis on patients and families, especially those who receive care at more than one facility.
HEALTH QUESTIONS

The following questions guided the development of this guideline:

1. What risk of acute phase AINV do antineoplastic therapies present to children with cancer?

2. Is the risk of AINV with multi-agent, single day antineoplastic therapy different than that of the most emetogenic antineoplastic given?

3. Is the risk of AINV with multiple day antineoplastic therapy regimens different than that of the most emetogenic antineoplastic therapy given on any individual day?

TARGET AUDIENCE

The target users of this guideline are all health care providers within Ontario who care for children and youth with cancer who are receiving antineoplastic medication and who are at risk of experiencing AINV. This guideline is aimed particularly at physicians, nurse practitioners, nurses, and pharmacists working in pediatric oncology centers and satellites in Ontario where pediatric oncology patients receive care. This guideline will also be of interest to clinicians in other jurisdictions, administrators, educators and researchers who provide care for children with cancer and/or who make decisions regarding resource availability, provide current professional education and/or frame questions for research in the realm of AINV.

METHODS

GUIDELINE DEVELOPMENT GROUP

The Pediatric Oncology Group of Ontario (POGO) identified AINV as a key supportive care initiative in 2008. The POGO AINV Guideline development group was formed in December 2008. Members were selected with a view to obtain interdisciplinary representation from several POGO institutions as well as content expertise. Experts who had published in the area of AINV in children or who had a current research interest in AINV or supportive care in cancer were invited to join the guideline development group.

LITERATURE SEARCH STRATEGY

In October and November 2008, the POGO Antineoplastic-induced Nausea and Vomiting (AINV) Guideline Development Group conducted a comprehensive literature review and environmental scan to identify guidelines for the classification of the emetogenicity of antineoplastic therapies for children and youth with cancer. It was also acknowledged that incorporation of the results of specific literature searches would be required in order to increase the applicability of the POGO guideline to children with cancer. Literature searches were conducted through November 2009. The searches were undertaken with the assistance of a library scientist; search details including search terms and limits for these searches are provided in Appendices A and B.

In brief, computerized literature searches of MEDLINE (OvidSP; 1950 to November Week 3 2009), Embase (OvidSP; 1980 to 2009 Week 51), Cumulative Index to Nursing & Allied Health Literature (CINHAL; OvidSP and EBSCOhost; 1980 to June Week 4, 2008), Cochrane Systematic Reviews, ACP Journal Club, DARE, CCTR, CMR, HTA and NHSEED (OvidSP) were performed. The search engine Google was utilized for identification of grey literature on the world-wide-web including local, provincial, national and international databases. Personal files of panel members were also reviewed for papers that merited inclusion in our results. In addition to the formal literature search strategy outlined above, panel members identified guidelines for the classification of the emetogenicity of antineoplastic agents for children and youth with cancer from their institutions as well as from other agencies and associations with which they had affiliations.
GUIDELINE AND EVIDENCE SELECTION CRITERIA

At the outset a guideline was sought which could be adapted to the POGO context. Each guideline identified through the search (Appendices A and B) was independently reviewed and scored by 4 to 6 members of the POGO AINV Guideline Development Panel using the Appraisal of Guidelines for Research & Evaluation (AGREE) instrument. The domains assessed by this instrument are: scope and purpose; stakeholder involvement; rigor; clarity and presentation; applicability, and editorial independence. The domain scores and overall assessments of each reviewer were aggregated and presented for discussion at a panel meeting held by teleconference. The suitability of each guideline for adaptation using the ADAPTE process was discussed by the panel. Reasons to support or refute adaptation of each guideline were provided. Rigor and applicability scores were emphasized in this discussion.

The guideline selected for adaptation, the source guideline, was to be updated by literature published since its development and, if necessary, with pediatric experience. Thus a literature search focused on the AINV experienced by children was conducted. Realizing that randomized controlled trials were not likely to compromise the majority of primary pediatric evidence in the AINV arena, all types of published evidence were included in this search. The experience of AINV by children who did not receive antiemetic prophylaxis or who received antiemetic prophylaxis which we now know to be inadequate would be weighted more highly than experience of children given effective antiemetic prophylaxis. Outcomes of interest included: proportion of children receiving antineoplastic therapy that attained complete AINV control (defined as either no vomiting and no nausea or no vomiting) during the acute phase and proportion of children receiving antineoplastic therapy that experienced failed AINV control (defined as 3 or more emetic episodes in 24 hours) during the acute phase.

Building on the framework of the source guideline, pediatric references using sources obtained through on-line database searches, references cited in the papers obtained through this search, papers gleaned from the personal files of panel members, and unpublished supplementary data from the research of panel members were evaluated for inclusion in the POGO guideline. Where the source guideline did not include an antineoplastic agent used in pediatric oncology and in the absence of other information, the emetogenicity ranking of one of the other guidelines previously identified and evaluated (see Appendix C) was employed.

DECISION PROCESS OF THE PANEL

In the event of contradictory information, panel members decided to take a conservative approach; that is, the higher emetogenicity risk ranking would be applied to an agent or combination of agents. This approach would be less likely to lead to breakthrough AINV and would perhaps allow reduction of antiemetic prophylaxis, if desired, in a patient who was well-controlled.

Decisions were taken through panel discussions and any differences in opinion were resolved by consensus. The quality of evidence and strength of recommendations were assessed using the system developed by Guyatt et al (see Appendix C) by the lead author and confirmed through discussion by the remaining panel members. If consensus was unable to be reached on any matter, a decision was made by the majority of panel members by a vote.

RESULTS

Six guidelines that were either developed for use in adults or for use in children using consensus-based or undisclosed methodologies were identified and assessed using the AGREE Instrument. The assessments are summarized in Appendix C. It was the unanimous decision to use the National Comprehensive Cancer Network’s (NCCN) guideline “Antiemesis v.2 2008” as the source guideline. It therefore was used as the framework for the development of guidelines for the classification of the emetogenic potential of antineoplastic medication in pediatric cancer patients using ADAPTE methods. Although based on adult data, the advantages of the NCCN guideline included its timeliness, inclusion of newer agents, and delineation of emetogenicity based on antineoplastic dose for many agents. When the NCCN guideline was recently updated, the newer version was compared to the previous version. Since the emetogenicity classification in newer version did not differ from that presented in the 2008 version, v3.2009 was cited as the source guideline. Panel members agreed to include all agents which appear in the NCCN guideline in the POGO guideline regardless of their current relevance to pediatric oncology since these agents may be administered to individual children with rare diseases or enter the pediatric domain at a later date.
Panel members also unanimously decided to adapt the Hesketh 1997 paper\textsuperscript{6} to inform the classification of combination antineoplastic therapies commonly used in pediatrics.

Based on the literature search that was conducted as described in the Methods section, gaps identified that required specific literature searches were:

- antineoplastic agents used in pediatric oncology (amsacrine, clofarabine, 6-mercaptopurine, thiopeta, vindesine) that do not appear in the source guideline
- antineoplastic agents with dose-dependent emetogenicity risk classifications that do not appear in the source guideline in consecutive dose increments, and
- antineoplastic agents whose classification in the source guideline is unclear (intravenous (IV) busulfan, oral (PO) busulfan for HSCT, etoposide).
QUESTION 1: WHAT RISK OF ACUTE PHASE AINV DO ANTINEOPLASTIC THERAPIES PRESENT TO CHILDREN WITH CANCER?

1. SINGLE ANTINEOPLASTIC AGENT THERAPY OF HIGH EMETIC RISK

The following single antineoplastic agents have high emetogenic potential:

- Altretamine
- *Carboplatin
- Carmustine > 250 mg/m²
- *Cisplatin
- *Cyclophosphamide ≥ 1 g/m²
- *Cytarabine 3 g/m²/dose
- Dacarbazine
- *Dactinomycin
- Mechlorethamine
- *Methotrexate ≥ 12 g/m²
- Procarbazine (oral)
- Streptozocin
- *Thiotepa ≥ 300 mg/m²

* pediatric evidence available and summarized in Table 1. 
Note: An alphabetical listing of antineoplastic agents and the emetic risk is provided in Appendix E.

Level of Evidence: low to very low 
Note: Level of evidence assigned by the authors of the source guideline to this recommendation was category 2A.

Grade of Recommendation: 1C
See Appendix C for key to levels of evidence and grades of recommendation.

Evidence

<table>
<thead>
<tr>
<th>Studies</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies where no antiemetic prophylaxis was given in at least one arm:</strong></td>
<td></td>
</tr>
</tbody>
</table>
| Hayes FA et al. 1981¹¹ | • observational study  
• 22 patients aged 0.8 to 18.1 yrs received cisplatin 90 mg/m² over 6 hours on day 1 followed by teniposide 100 mg/m² on day 3 were evaluated during 2 separate cycles  
• no antiemetic prophylaxis mentioned  
• 1 child did not vomit during cisplatin infusion |
| Komada Y et al. 1999¹² | • observational study  
• 25 children aged 1 to 14 yrs given cytarabine 3 g/m² with no antiemetic prophylaxis  
• no vomiting observed in 8% of children |
| Saarinen UM et al. 1991¹³ | • observational study  
• 9 children undergoing conditioning for bone marrow transplant with thiotepa 375 mg/m²/day for 3 consecutive days given no antiemetic prophylaxis; 2 children received 2 transplants with this conditioning  
• no vomiting observed in 3/9 children (33%) and 5/11 courses (45%)  
• time frame of vomiting relative to thiotepa administration not described |
| Sumer T et al.¹⁴ 1988 | • randomized cross-over study  
• 11 children aged 16 to 65 months receiving cisplatin 45 mg/m² over 2 hours daily x 2 days randomized to receive dexamethasone for AINV prophylaxis or no prophylaxis on first cycle. Dexamethasone given on alternating cycles thereafter  
• no vomiting observed on day 1 in 3/11 (27%) patients when dexamethasone given and in 0/11 patients when no AINV prophylaxis given |
Table 1: Summary of Pediatric Evidence Used to Inform Recommendation 1 (continued)

<table>
<thead>
<tr>
<th>Studies</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies where antiemetic prophylaxis was given:</strong></td>
<td></td>
</tr>
<tr>
<td>Berrak SG et al. 2007 (^15)</td>
<td>• randomized, double blind, cross over study&lt;br&gt;• 18 patients (1 to 23 yrs) randomly received 1 of 2 granisetron doses on alternating courses of carboplatin 175 mg/m(^2) - containing therapy&lt;br&gt;• 225 treatment courses evaluated, some of which may have included vincristine&lt;br&gt;• no vomiting or nausea observed on day 1 in 95/121 (79%) of courses when high dose granisetron given and in 72/104 (69%) of courses when low dose granisetron given</td>
</tr>
<tr>
<td>Hewitt M et al. 1991 (^16)</td>
<td>• observational study&lt;br&gt;• administered cyclophosphamide 50 or 60 mg/kg/day (1500-1800 mg/m(^2)/day) to 15 children aged 2 to 17 yrs prior to bone marrow transplant&lt;br&gt;• ondansetron given for AINV prophylaxis&lt;br&gt;• children experienced no vomits or retches on 60% of days where cyclophosphamide was given</td>
</tr>
<tr>
<td>Holdsworth MT et al. 2006 (^2) (supplementary data)</td>
<td>• observational study&lt;br&gt;• validated nausea/vomiting survey administered to 224 children over 1256 courses of antineoplastic therapy&lt;br&gt;• ondansetron +/- dexamethasone given for AINV prophylaxis&lt;br&gt;• complete response defined as no vomiting, retching or nausea&lt;br&gt;• complete emetic control observed in &lt; 80% of children receiving first course of: cisplatin ≥ 90 mg/m(^2) (13 patients; 27 courses), cyclophosphamide ≥ 1 g/m(^2) (21 patients; 40 courses), cytarabine 3 g/m(^2) q12h (9 patients; 13 courses), cytarabine 3 g/m(^2) q12h (8 patients; 25 courses), carboplatin 175 mg/m(^2) (6 patients; 63 courses), dactinomycin (5 patients; 8 courses), methotrexate 12 g/m(^2) (7 patients; 26 courses)</td>
</tr>
<tr>
<td>Kusnierczyk NMA et al. 2002 (^17) (supplementary data)</td>
<td>• observational study&lt;br&gt;• 25 children undergoing conditioning for bone marrow transplant with various regimens given ondansetron + dexamethasone for AINV prophylaxis&lt;br&gt;• no vomiting observed in 8/9 (89%) of children on first day of administration of cyclophosphamide 50 mg/kg/day</td>
</tr>
<tr>
<td>Lafay-Cousin L et al. 2000 (^18)</td>
<td>• observational study&lt;br&gt;• 18 children undergoing conditioning for bone marrow transplant with thiotepa 300 mg/m(^2)/day for 3 consecutive days given ondansetron for AINV prophylaxis&lt;br&gt;• no vomiting observed in 4 children (22%)&lt;br&gt;• timeframe of vomiting relative to thiotepa administration unknown</td>
</tr>
<tr>
<td>Miyajima Y et al. 1994 (^19)</td>
<td>• non-randomized cross-over study&lt;br&gt;• 22 children receiving 1 of 3 antineoplastic regimens on 2 consecutive cycles and randomized to receive either metoclopramide + promethazine or granisetron in cross-over design&lt;br&gt;• no vomiting observed in 80% of cycles of cytarabine 3 g/m(^2) and in 48% of cycles of cisplatin 90 mg/m(^2) given granisetron prophylaxis&lt;br&gt;• no vomiting observed in 0% of courses where metoclopramide + promethazine given as AINV prophylaxis</td>
</tr>
<tr>
<td>Nahata MC et al 1996 (^20)</td>
<td>• non-randomized study&lt;br&gt;• 17 children undergoing conditioning for bone marrow transplant given ondansetron and other antiemetics&lt;br&gt;• 5 children received thiotepa for 3 consecutive days in a dose of either 300 mg/m(^2)/dose (3 patients) or 200 mg/m(^2)/dose (2 patients)&lt;br&gt;• no vomiting observed on 5/15 days that thiotepa was given overall; 300 mg/m(^2)/dose: 3/9 days and 200 mg/m(^2)/dose: 2/6 days</td>
</tr>
</tbody>
</table>
Available pediatric experience confirms the source guideline’s ranking of cisplatin $\geq 50$ mg/m$^2$ and cyclophosphamide $> 1.5$ g/m$^2$ as highly emetogenic antineoplastic agents when given as single agents. Changes from the source guideline are:

- **addition of** carboplatin, cytarabine 3 g/m$^2$, dactinomycin, methotrexate $\geq 12$ g/m$^2$ and thiotepa $\geq 300$ mg/m$^2$,
- **reduction of the** cyclophosphamide dose threshold from $\geq 1.5$ g/m$^2$ to $\geq 1$ g/m$^2$, and
- **inclusion of** cisplatin regardless of dose.

### Carboptatin

The determination of the risk of nausea and vomiting associated with carboplatin administration was complicated by contradictory evidence. The incidence of vomiting and nausea was prospectively evaluated during a single, one-day treatment course in 30 children with solid tumors aged 2 to 16 years. Of these, 6 patients aged 2 to 8 years received carboplatin (5 – 600 mg/m$^2$) alone while another 6 patients received multi-agent antineoplastic treatment that included carboplatin. All children received ondansetron every 8 hours for 5 days from the start of antineoplastic therapy. AINV was evaluated daily for 5 days. Nausea severity was assessed by the parent using an unvalidated, 3-point questionnaire. Results are reported for the entire carboplatin group; results are not available for those patients receiving single-agent carboplatin therapy. During the acute phase, 11 of 12 patients receiving carboplatin either did not vomit or vomited no more than twice. Thus, no vomiting was observed in either 5 of the 6 or all of the single-agent carboplatin recipients (83 or 100%). This level of response to ondansetron prophylaxis would place carboplatin as a moderate-risk emetogen.

Holdsworth et al prospectively evaluated AINV in 6 children over 63 courses of carboplatin 175 mg/m$^2$. AINV was assessed using a validated instrument that was completed by either the child or their parent. All children receiving carboplatin 175 mg/m$^2$ received ondansetron and dexamethasone as AINV prophylaxis. Complete control of both nausea and vomiting during the acute phase was observed in 60 to 83% of courses. This level of response to ondansetron plus dexamethasone prophylaxis would place carboplatin as a high-risk emetogen.

The efficacy of two granisetron doses was evaluated in a randomized double-blind cross-over study in 18 patients aged 1 to 23 years of age (median: 7.7 years) over 225 courses of carboplatin 175 mg/m$^2$ with or without vincristine. The number of pediatric patients included and the number of courses where carboplatin was given as a single agent are unknown. AINV was assessed by either the patients or parents; the nausea...
severity assessment instrument was not described. Complete protection from nausea and vomiting was observed in the acute phase in 95 (79%) and 72 (69%) courses after administration of granisetron 40 mcg/kg and 10mcg/kg, respectively. This level of response to granisetron prophylaxis would place carboplatin as a high-risk emetogen.

Given the very small numbers of patients evaluated, the use of unvalidated or unknown nausea severity assessment instruments in the 2 studies supporting the classification of carboplatin as a moderate emetogen and the prevailing conservative philosophy of the guideline development panel, carboplatin was ranked as a highly emetogenic agent.

**Cisplatin**

The source guideline ranks cisplatin as a high-risk emetogen at doses of 50 mg/m² or more. This finding was confirmed by pediatric experience. In addition, investigators described poor AINV control associated with cisplatin doses less than 50 mg/m². Sumer et al conducted a randomized cross-over study to compare AINV associated with cisplatin 45 mg/m² given over 2 hours with or without dexamethasone prophylaxis. The number of vomits was recorded by nurses; nausea severity was not assessed. Of the 11 children studied, all vomited within 24 hours of the cisplatin dose when no AINV prophylaxis was provided. This incidence of AINV would place cisplatin 45 mg/m² as a high-risk emetogen.

The control of AINV afforded by tropisetron was evaluated in an observational study of 22 children given 125 antineoplastic courses, 17 of which contained cisplatin 20 or 120 mg/m². The method of nausea severity assessment was not disclosed. In 5 of 10 cisplatin-containing courses where tropisetron plus dexamethasone were given for AINV prophylaxis, no acute phase vomiting or nausea were observed. All 7 cisplatin-containing courses given AINV prophylaxis with tropisetron alone were associated with vomiting or nausea during the acute phase. It is not possible to conclusively determine responses to the low dose cisplatin courses in this study. However, it appears that dexamethasone was not given with these courses. Therefore, although not explicitly stated by the investigators, it is assumed that administration of cisplatin 20 mg/m² with tropisetron prophylaxis was associated with an AINV incidence of 100%. This level of response to tropisetron prophylaxis would place cisplatin 20 mg/m² as a high-risk emetogen.

**Cyclophosphamide**

Several pediatric studies have confirmed the high emetogenicity of cyclophosphamide in doses of 1.5 g/m² (50 mg/kg) or more. Yet, a high prevalence of AINV was observed by Holdsworth et al after administration of cyclophosphamide in doses of 1 to less than 2 g/m² (33 to less than 67 mg/kg). Of 21 patients receiving 40 courses of single agent cyclophosphamide therapy and given ondansetron plus dexamethasone for AINV prophylaxis, complete control of nausea and vomiting was achieved in 57% of patients during the acute phase of the first study cycle and 75% on the second study cycle. The proportion of patients or cycles receiving cyclophosphamide doses between 1 and 1.5 g/m² is unknown. In keeping with the conservative philosophy of the guideline development panel, the decision was made to consider cyclophosphamide in doses of ≥ 1 g/m² as highly emetogenic.

**Cytarabine**

A non-randomized cross-over study was conducted to compare the efficacy of granisetron vs conventional AINV prophylaxis (metoclopramide plus promethazine). The number of vomits was recorded by parents or nursing staff for at least 48 hours after antineoplastic administration. A parent or member of the nursing staff also evaluated nausea severity using an undisclosed instrument. The duration of monitoring is unclear (24 or 48 hours). All of the 10 children who received cytarabine 3 g/m² and conventional AINV prophylaxis vomited during the monitoring period. This level of response to metoclopramide plus promethazine prophylaxis would place cytarabine 3 g/m² as a high-risk emetogen.

Komada et al conducted a randomized, non-blinded study to evaluate granisetron that incorporated a screening phase where no antiemetic prophylaxis was given to children receiving cytarabine 3 g/m² on day 1, daunorubicin and L-asparaginase on day 3 and oral dexamethasone from day 1 through 7. The number of vomits and retches were recorded. Nausea severity was not assessed. Twenty-three of the 25 patients (92%) screened vomited, though the timing of the emesis (i.e. after day 1 or at any time during the study period) was not disclosed. Although not given for the purpose of AINV prophylaxis, dexamethasone may well have provided some degree of protection. This level of response to dexamethasone prophylaxis would place cytarabine 3 g/m² as a high-risk emetogen.
In the above-mentioned observational study by Holdsworth et al, 4 of 9 children (44%) who received cytarabine 3 g/m² q12h with ondansetron prophylaxis experienced complete control of both nausea and vomiting during the acute phase. Complete control of acute phase AINV was observed in 75 and 67% of courses of the same antineoplastic regimen given to 8 children with ondansetron plus dexamethasone prophylaxis. Again, this level of response to ondansetron +/- dexamethasone prophylaxis would place cytarabine 3 g/m² as a high-risk emetogen.

**Dactinomycin**
A single study was identified that described dactinomycin-associated AINV. This previously described study by Holdsworth et al observed complete control of both acute phase vomiting and nausea in 4 of 5 patients receiving dactinomycin 45 µg/kg with ondansetron plus dexamethasone as prophylaxis. This level of response to ondansetron plus dexamethasone prophylaxis would place dactinomycin as a high-risk emetogen.

**Methotrexate ≥ 12 g/m²**
The AINV experience of 7 children receiving 26 courses of methotrexate 12 g/m² was observed by Holdsworth et al in the aforementioned study. With ondansetron plus dexamethasone given as AINV prophylaxis, 57 or 60% of patients achieved complete control of both vomiting and nausea during the acute phase of a study course. This level of response to ondansetron plus dexamethasone prophylaxis would place methotrexate 12 g/m² as a high-risk emetogen.

**Thiotepa**
Three studies were identified that provided information regarding the incidence of emesis following thiotepa administration to children. The first described a 33% response rate (based on number of study days that were free of emesis) in 3 children given thiotepa 300 mg/m²/day for 3 consecutive days prior to HSCT and in 2 children given 200 mg/m²/day. All children were given ondansetron for AINV prophylaxis. Nausea was not assessed.

Similarly, Lafay-Cousin et al described a complete protection rate of 22% in 18 children who received thiotepa 300 mg/m²/day again for HSCT conditioning and ondansetron. The dose of ondansetron administered is unknown as is the time frame of observation of vomiting.

Saarinen et al observed no vomiting in 33% of children (3/9) or 45% of courses (5/11) of thiotepa 375 mg/m²/day for 3 consecutive days given without antiemetic prophylaxis to children prior to autologous transplant. Nausea was not assessed. The duration of observation relative to thiotepa administration is unknown.

Although the number of children whose emetic response to thiotepa has been evaluated is small, the inability of ondansetron to completely protect children from vomiting suggests that it presents a high emetic risk, at least in doses of 300 mg/m² or more.

**Research Gaps**
No pediatric literature was located regarding the risk of AINV in children receiving altretamine, carmustine > 250 mg/m², dacarbazine, mechlorethamine, oral procarbazine, or streptozocin. Since the existing pediatric evidence is derived from a very small number of patients and nausea severity assessment was often not included as a study endpoint or was assessed using an unvalidated instrument, additional pediatric evidence is required to improve confidence in all the recommended emetogenicity rankings. In particular, the propensities of carboplatin, cisplatin < 50 mg/m², cyclophosphamide 1 to ≤ 1.5 g/m², dactinomycin and methotrexate ≥ 12 g/m² to cause AINV require clarification.
2. SINGLE ANTINEOPLASTIC AGENT THERAPY OF MODERATE EMETIC RISK

The following single antineoplastic agents have moderate emetogenic potential:

- Aldesleukin > 12 to 15 million units/m²
- Amifostine > 300 mg/m²
- Arsenic trioxide
- Azacitidine
- Bendamustine
- Busulfan > 4 mg/day
- *Carmustine ≤ 250 mg/m²
- *Clofarabine
- *Cyclophosphamide < 1 g/m²
- Cyclophosphamide (oral)
- Cytarabine > 200 mg/m² to < 3 g/m²
- *Daunorubicin
- *Doxorubicin
- Epirubicin
- Etoposide (oral)
- Idarubicin
- Ifosfamide
- Imatinib (oral)
- *Intrathecal therapy (methotrexate, hydrocortisone and cytarabine)
- Irinotecan
- Lomustine
- Melphalan > 50 mg/m²
- Methotrexate 250 mg/m² to < 12 g/m²
- Oxaliplatin > 75 mg/m²
- Temozolomide (oral)
- Vinorelbine (oral)

* Pediatric evidence available and summarized in Table 2.

Note: An alphabetical listing of antineoplastic agents and the emetic risk is provided in Appendix E.

Level of Evidence: low to very low
Note: Level of evidence assigned by the source guideline to this recommendation was category 2A.

Grade of Recommendation: 1C
See Appendix C for key to levels of evidence and grades of recommendation.

Evidence

Table 2: Summary of Evidence Used to Inform Recommendation 2

<table>
<thead>
<tr>
<th>Studies</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies where no antiemetic prophylaxis was given in at least one arm:</strong></td>
<td></td>
</tr>
<tr>
<td>Holdsworth MT et al. 1998²³</td>
<td>• observational study</td>
</tr>
<tr>
<td></td>
<td>• nausea and vomiting were assessed in 37 children (1 to 17 yrs) after receipt of 87 <strong>triple intrathecal</strong> antineoplastic (methotrexate, hydrocortisone, cytarabine) injections with no antiemetic prophylaxis</td>
</tr>
<tr>
<td></td>
<td>• no vomiting observed in 8/37 (22%) of patients within the first 24 hours</td>
</tr>
<tr>
<td></td>
<td>• no nausea or vomiting observed in 5/37 (13%) of patients within the first 24 hours</td>
</tr>
<tr>
<td>Jeha S et al. 2004²⁴</td>
<td>• phase I study of <strong>clofarabine</strong> 11.25 to 70 mg/m²/day for 5 days</td>
</tr>
<tr>
<td></td>
<td>• 25 patients evaluated aged 1 to 19 years</td>
</tr>
<tr>
<td></td>
<td>• no information regarding AINV prophylaxis provided, if any</td>
</tr>
<tr>
<td></td>
<td>• no nausea or vomiting observed in 6 patients (24%) overall and in 4 of 13 (31%) patients receiving clofarabine 52 mg/m²/day</td>
</tr>
<tr>
<td>Jeha S et al. 2006²⁵</td>
<td>• phase II study of <strong>clofarabine</strong> 52 mg/m²/day for 5 days</td>
</tr>
<tr>
<td></td>
<td>• 61 patients aged 1 to 20 years each received 1 to 11 cycles</td>
</tr>
<tr>
<td></td>
<td>• no information regarding AINV prophylaxis provided; some patients received corticosteroid on days 1 to 3 of some cycles</td>
</tr>
<tr>
<td></td>
<td>• grade 3 or higher nausea observed in 10 of 122 cycles</td>
</tr>
<tr>
<td>Parker RI et al. 2001²⁶</td>
<td>• randomized, double-blind, cross-over placebo controlled trial</td>
</tr>
<tr>
<td></td>
<td>• 26 children (2 to 17 yrs) given 146 <strong>triple intrathecal</strong> antineoplastic doses (22 patients: methotrexate + hydrocortisone + cytarabine; 4 patients: methotrexate)</td>
</tr>
<tr>
<td></td>
<td>• efficacy of 2 doses of ondansetron compared against placebo</td>
</tr>
<tr>
<td></td>
<td>• no vomiting observed in 32/51 (63%) of intrathecal treatments when placebo given</td>
</tr>
</tbody>
</table>
### Table 2: Summary of Evidence Used to Inform Recommendation 2 (continued)

<table>
<thead>
<tr>
<th>Studies</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies where antiemetic prophylaxis was given:</strong></td>
<td></td>
</tr>
<tr>
<td>Dupuis LL et al. 1999&lt;sup&gt;27&lt;/sup&gt;</td>
<td>• observational study&lt;br&gt;• acute vomiting and nausea assessed in 94 children (1 to 17.7 yrs) with acute lymphoblastic leukemia&lt;br&gt;• no vomiting observed in most children who received <strong>doxorubicin</strong> given ondansetron as AINV prophylaxis</td>
</tr>
<tr>
<td>Holdsworth MT et al. 1995&lt;sup&gt;28&lt;/sup&gt;</td>
<td>• observational study&lt;br&gt;• nausea and vomiting assessed in 16 children (2 to 15 yrs) with acute lymphoblastic leukemia over 319 courses&lt;br&gt;• each course given with or without ondansetron at clinicians’ discretion&lt;br&gt;• 149 courses given with no antiemetic prophylaxis&lt;br&gt;• no vomiting seen in 8/27 (30%) of carmustine 60 mg/m&lt;sup&gt;2&lt;/sup&gt; courses and in 14/34 (41%) of <strong>cyclophosphamide</strong> 600 mg/m&lt;sup&gt;2&lt;/sup&gt; courses when no antiemetic prophylaxis given</td>
</tr>
<tr>
<td>Holdsworth MT et al. 2006&lt;sup&gt;2&lt;/sup&gt; (supplementary data)</td>
<td>• observational study&lt;br&gt;• validated nausea/vomiting survey administered to 224 children over 1256 courses of antineoplastic therapy&lt;br&gt;• ondansetron +/- dexamethasone given for AINV prophylaxis&lt;br&gt;• complete response defined as no vomiting, retching or nausea&lt;br&gt;• complete response observed in 76% of 29 children receiving first course of <strong>doxorubicin</strong> 25 mg/m&lt;sup&gt;2&lt;/sup&gt; or <strong>daunomycin</strong> 30 mg/m&lt;sup&gt;2&lt;/sup&gt; receiving ondansetron</td>
</tr>
</tbody>
</table>

### Discussion

Available pediatric experience confirms the source guideline’s ranking of carmustine ≤ 250 mg/m<sup>2</sup>, cyclophosphamide ≤ 1 g/m<sup>2</sup>, daunorubicin and doxorubicin as moderately emetogenic antineoplastic agents when given as single agents. Changes from the source guideline<sup>10</sup> are:

- removal of the dose-dependent classification (> 4 mg/day) of IV busulfan emetogenicity;
- deletion of cisplatin < 50 mg/m<sup>2</sup>, carboplatin, and dactinomycin (see recommendation 1);
- capping the cytarabine dose at 3 g/m<sup>2</sup> (see recommendation 1);
- reduction of the minimum cytarabine dose from 1 g/m<sup>2</sup> to > 200 mg/m<sup>2</sup>; and
- addition of clofarabine and triple intrathecal therapy.

### Busulfan IV

The source guideline did not explicitly include information regarding IV busulfan.<sup>9</sup> Busulfan in doses > 4 mg/day was ranked as a moderate emetic risk while busulfan (no dose provided) was ranked as a minimal emetic risk. In neither case was the route of administration described. Busulfan IV is typically given to children as part of HSCT conditioning in initial doses ranging from 3.2 to 4.8 mg/kg/day.<sup>29</sup> Thus the dose ceiling of 4 mg/day stipulated in the source guideline is not relevant to pediatric practice and was removed. The Busulfex<sup>®</sup> product monograph describes a 43% incidence of vomiting during IV busulfan administration.<sup>30</sup> Information regarding the type of AINV prophylaxis provided in these studies is not provided. Based on this information, IV busulfan at any dose is ranked as a moderate emetogen.
Clofarabine
Of the guidelines identified in the search for a source guideline for adaptation, only the guideline of the Children's Oncology Group included clofarabine and ranked it as a moderate emetogen with a frequency of emesis of 60 to 90%. Despite being an agent indicated solely for pediatric use, published experience regarding the risk of nausea and vomiting associated with clofarabine is scant. The product monograph states that clofarabine is a moderate emetogen but does not describe this further.31 The incidences of nausea and vomiting provided in the product monograph are 73% and 78% respectively though no time frame is given for this information, nor is it known whether observations were made in the absence or presence of AINV prophylaxis.

Jeha et al conducted phase I and II trials to evaluate toxicity and efficacy of clofarabine in children with relapsed leukemia.24, 25 Information regarding the administration of antiemetic prophylaxis is not provided; however, in the later trial25, corticosteroids were administered during some study cycles on days 1 to 3 to prevent systemic inflammatory response symptoms. Nausea and vomiting were evaluated as per the National Cancer Institute Common Toxicity Criteria version 2.0 in both studies. The methods of assessment of nausea or vomiting were not described in either study. In addition, the duration of nausea and vomiting assessment was not provided. Nevertheless, nausea or vomiting were reported in 19 of 25 patients (76%) receiving clofarabine in the phase I study.24 Nausea of grade 3 or higher (i.e. leading to inadequate oral caloric/fluid intake requiring supplementation, life-threatening consequences, or death) was reported after 10 of 122 treatment cycles in the phase II.25

Assuming that the frequency of acute phase AINV associated with clofarabine is 70 to 80% in the absence of AINV prophylaxis and in keeping with the conservative philosophy of the guideline development panel, clofarabine was ranked as a moderate-risk emetogen.

Cytarabine
The source guideline had no provision for cytarabine doses > 200 mg/m² and < 1 g/m². In keeping with the guideline development panel's desire to eliminate such gaps and with its conservative philosophy, cytarabine < 200 mg/m² to < 1 g/m² was classified as a moderate emetogen.

Intrathecal Therapy: Methotrexate, Cytarabine and Hydrocortisone
The prevalence of nausea and vomiting associated with triple agent (methotrexate, cytarabine and hydrocortisone) intrathecal (TIT) administration has been assessed in children. Nausea and vomiting experienced during the week following triple intrathecal administration were recorded by 63 children or their parent using a validated survey.23 Results were presented as a combination of the acute and delayed phases. Children received either ondansetron for AINV prophylaxis or no prophylaxis throughout their course of therapy as dictated by the medical team. 37 children received at least one TIT dose without AINV prophylaxis. Of these, complete control of both nausea and vomiting were observed in 5 patients (14%). Though it is not possible to distinguish the acute vs delayed phase responses, the authors state that nausea and vomiting typically presented 3 to 4 hours after the TIT was administered and usually had resolved 24 hours later. This incidence of AINV would place TIT as a moderate-risk emetogen.

Similarly, Parker et al26 randomized 26 children aged 2 to 17 years to receive one of 3 interventions (placebo, lower dose ondansetron and higher dose ondansetron) prior to TIT administration in a cross-over fashion up to 6 times. Parents recorded the number of times their children vomited for 48 hours after the TIT was administered. Placebo was administered on 51 occasions to 25 patients; vomiting was observed after 32 (63%) TIT treatments when placebo was given. This incidence of AINV confirms the classification of TIT as a moderate-risk emetogen.

Research Gaps
No pediatric literature was located regarding the risk of AINV in children receiving aldesleukin, amifostine, arsenic trioxide, azacitidine, bendamustine, IV busulfan, cyclophosphamide (oral), cytarabine 1 to < 3 g/m², idarubicin, ifosfamide, imatinib (oral), irinotecan, lomustine, melphalan > 50 mg/m², methotrexate 250 to < 12 g/m², oxaliplatin > 75 mg/m², temozolomide (oral) or vinorelbine (oral). Since the existing pediatric evidence is derived from a small number of patients and nausea severity assessment was often not included as a study endpoint or was assessed using an unvalidated instrument, additional pediatric evidence is required to improve confidence in all the recommended emetogenicity rankings. In particular, the risk of AINV following
intrathecal administration of medications other than the combination of methotrexate, cytarabine and hydrocortisone and the emetogenicity of cytarabine doses $>$ 200 mg/m$^2$ to $<$ 1 g/m$^2$ merit study.

The range of emetic potential encompassed in the category of moderately emetogenic (30 to 90% risk) is overly broad. More pediatric experience is required to more fully inform the risk of AINV with these agents and to distinguish those which are truly moderate emetogens (e.g. 30 to 60% risk) from those which carry a moderately high risk (e.g. 60 to 90% risk).

3. **SINGLE ANTINEOPLASTIC AGENT THERAPY OF LOW EMETIC RISK**

The following single antineoplastic agents have low emetogenic potential:

- Amifostine $\leq$ 300 mg/m$^2$
- Amscarine
- Bexarotene
- *Busulfan (oral)*
- Capcicitabine
- Cytarabine $\leq$ 200 mg/m$^2$
- Docetaxel
- Doxorubicin (liposomal)
- Etoposide
- Fludarabine (oral)
- 5-Fluorouracil
- Gemcitabine
- Ixabepilone
- Methotrexate $>$ 50 mg/m$^2$ to $<$ 250 mg/m$^2$
- Mitomycin
- Mitoxantrone
- Nilotinib
- Paclitaxel
- Paclitaxel-albumin
- Pemetrexed
- Teniposide
- Thiopeta $<$ 300 mg/m$^2$
- Topotecan
- Vorinostat

Note: An alphabetical listing of antineoplastic agents and the emetic risk is provided in Appendix E.

**Level of Evidence**: very low

*Note: Level of evidence assigned by the authors of the source guideline to this recommendation was category 2A.*

**Grade of Recommendation**: 1C

*See Appendix C for key to levels of evidence and grades of recommendation.*

**Evidence**

<table>
<thead>
<tr>
<th>Studies</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies where no antiemetic prophylaxis was given in at least one arm:</strong></td>
<td></td>
</tr>
<tr>
<td>Hayes FA et al. 1981$^{11}$</td>
<td>observational study</td>
</tr>
<tr>
<td></td>
<td>22 patients aged 0.83 to 18.1 yrs received cisplatin 90 mg/m$^2$ over 6 hours on day 1 followed by teniposide 100 mg/m$^2$ on day 3 were evaluated during 2 separate cycles</td>
</tr>
<tr>
<td></td>
<td>no antiemetic prophylaxis mentioned</td>
</tr>
<tr>
<td></td>
<td>no vomiting observed with teniposide</td>
</tr>
<tr>
<td><strong>Studies where antiemetic prophylaxis was given:</strong></td>
<td></td>
</tr>
<tr>
<td>Kusnierczyk NMA et al. 2002$^{17}$ (supplementary data)</td>
<td>observational study</td>
</tr>
<tr>
<td></td>
<td>25 children undergoing conditioning for HSCT with various regimens given ondansetron for AINV prophylaxis on days when oral busulfan given</td>
</tr>
<tr>
<td></td>
<td>no vomiting observed in 6/7 (86%) of children during 4-day oral busulfan course and on 25/28 (89%) of days that oral busulfan given</td>
</tr>
</tbody>
</table>
**Discussion**

No pediatric experience was identified that was applicable to the determination of agents of low emetic risk other than for oral busulfan. Based on their clinical experience, members of the POGO AINV Guideline Development Panel were concerned that the emetogenicity of IV etoposide was dose-dependent and that higher doses were moderately emetogenic. Indeed, the COG Supportive Care Guidelines rank IV etoposide 1800 mg/m$^2$ / total dose given during HSCT conditioning as a high risk emetogen (60-90% incidence of vomiting). However, no specific literature could be identified to support the higher classification of high dose IV etoposide and the ranking of the source guideline was retained. Changes from the source guideline are:

- addition of teniposide and thiota < 300 mg/m$^2$ based on the COG Supportive Care Guidelines;
- addition of amsacrine and oral busulfan; and
- increasing the minimum cytarabine dose from 100 mg/m$^2$ to 200 mg/m$^2$ to ≤ 200 mg/m$^2$.

**Amsacrine**

Due to the lack of published pediatric experience regarding the emetogenicity of amsacrine, the other guidelines which were identified in the process of selecting the source guideline for adaptation were consulted. Amsacrine was not listed in any of these documents. Cancer Care Ontario and the British Columbia Cancer Agency state the incidence of vomiting due to amsacrine to be 10 to 30% and 10%, respectively. Based on this information, amsacrine was ranked as a low risk emetogen.

**Busulfan (Oral)**

The source guideline did not explicitly include information regarding oral busulfan. Busulfan in doses > 4 mg/day was ranked as entailing a moderate emetic risk while busulfan (no dose provided) was ranked as a minimal emetic risk. In neither case was the route of administration described. Supplementary data obtained from Kusnierczyk et al support the assignment of oral busulfan given as part of HSCT conditioning as being of low emetic risk. These children received ondansetron q12h during the 4 days of oral busulfan administration. Children did not vomit during 6 of 7 oral busulfan courses and were protected from vomiting on 25 of 28 days when oral busulfan was administered.

**Cytarabine**

The source guideline had no provision for cytarabine doses < 100 mg/m$^2$. In keeping with the guideline development panel’s desire to eliminate such gaps and with its conservative philosophy, cytarabine < 100 mg/m$^2$ was classified as a low-risk emetogen.

**Teniposide**

Teniposide was not included in the source guideline. A single study was identified in the literature regarding vomiting or nausea attributable to teniposide experienced by children. The aim of the study conducted by Hayes et al was to evaluate the effect of cisplatin on magnesium; vomiting associated with both cisplatin (day 1) and teniposide (day 3) was reported. Nausea was not reported. It appears that no antiemetic prophylaxis was provided. The investigators report that “no vomiting occurred with teniposide”. The time frame of this observation relative to teniposide administration is unknown. Both Cancer Care Ontario and the Children’s Oncology Group Supportive Care Guidelines classify teniposide as an emetogen of low potency. In the absence of specific evidence, teniposide was classified as being of low emetogenic potential in the POGO guideline.

**Thiotepa**

Thiotepa ≥ 300 mg/m$^2$ has been classified as a high-risk emetogen (see recommendation 1). Thiotepa at any dose was not included in the source guideline. In alignment with the desire to avoid gaps in the dose range of agents included in this guideline, thiota in lower doses of was classified as a low-risk emetogen based on its classification in the COG Supportive Care Guidelines.
Research Gaps

The lack of pediatric information which is available to inform the emetogenicity classification of agents deemed to be of low emetic risk in adults is glaring. The need for information specific to children is especially pressing for antineoplastic agents that are commonly used in pediatric treatment protocols such as amsacrine, cytarabine < 200 mg/m², methotrexate 50 mg/m² to < 250 mg/m², mitoxantrone, paclitaxel, etoposide, teniposide, thiopeta and topotecan. The potential dose-dependent emetogenicity of IV etoposide merits investigation. The emetogenicity of oral busulfan also requires more rigorous evaluation.

4. SINGLE ANTEINEOPLASTIC AGENT THERAPY OF MINIMAL EMETIC RISK

The following single antineoplastic agents have minimal emetogenic potential:

- Alemtuzumab
- Alpha interferon
- Asparaginase (IM or IV)
- Bevacizumab
- Bleomycin
- Bortezomib
- Cetuximab
- Chlorambucil (oral)
- Cladribine (2-chlorodeoxyadenosine)
- Decitabine
- Denileukin difitox
- Dasatinib
- Dexrazoxane
- Erlotinib
- Fludarabine
- Gefitinib
- Gemtuzumab ozogamicin
- Hydroxyurea (oral)

- Lapatinib
- Lenalidomide
- Melphalan (oral low-dose)
- Mercaptopurine (oral)
- Methotrexate ≤ 50 mg/m²
- Nellarine
- Panitumumab
- Pentostatin
- Rituximab
- Sorafenib
- Sunitinib
- Temsirolimus
- Thalidomide
- Thioguanine (oral)
- Trastuzumab
- Valrubicin
- Vinblastine
- Vincristine
- Vinodesine
- Vinorelbine

Note: An alphabetical listing of antineoplastic agents and the emetic risk is provided in Appendix E.

Level of Evidence: very low

Note: Level of evidence assigned by the authors of the source guideline to this recommendation was category 2A.

Grade of Recommendation: 1C
See Appendix C for key to levels of evidence and grades of recommendation.

Discussion

No pediatric experience was identified that was applicable to the determination of agents of minimal emetic risk. The list of minimal emetogens in the source guideline included asparaginase but did not differentiate between the various asparaginase products available: native asparaginase, Erwinia asparaginase or Peg-asparaginase. An attempt to locate literature specific to the emetogenicity of Peg-asparaginase was made (see Appendix A) but none was located. The ranking of the source guideline was therefore accepted and interpreted to be applicable to all available asparaginase products. Literature regarding AINV experienced by children receiving oral mercaptopurine and vindesine was specifically sought but none was identified. The Children’s Oncology Group Supportive Care Guidelines classify both of these agents as emetogens of minimal potency. In the absence of specific evidence, this classification was adopted in the POGO guideline. Changes from the source guideline are:

- deletion of busulfan (see recommendations 2 and 3), and
- addition of mercaptopurine (oral) and vindesine (as per COG Supportive Care Guidelines).
Research Gaps

No information was identified that confirms or refutes the emetogenicity classification of agents deemed to be of minimal emetic risk in adults for application to pediatric practice. Once again, the need for information specific to children is especially pressing for antineoplastic agents that are often included in pediatric treatment protocols such as asparaginase, bleomycin, cladribine, fludarabine, gemtuzumab, hydroxyurea, mercaptopurine (oral), methotrexate ≤ 50 mg/m², Peg-asparaginase, rituximab, thioguanine (oral), vinblastine, vincristine, vindesine, and vinorelbine.

QUESTION 2: IS THE RISK OF AINV WITH MULTI-AGENT, SINGLE DAY ANTINEOPLASTIC THERAPY DIFFERENT THAN THAT OF THE MOST EMETOGENIC ANTINEOPLASTIC GIVEN?

5. MULTIPLE AGENT ANTINEOPLASTIC THERAPY

With the exceptions noted below, the emetogenicity of multiple agent antineoplastic therapy is classified based on the emetic risk of the most highly emetogenic agent in the combination to be given. The emetic risk of specific multi-agent antineoplastic regimens is as follows:

<table>
<thead>
<tr>
<th>Level of Emetic Risk</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>• *cyclophosphamide + etoposide&lt;br&gt;• *cytarabine 150-200 mg/m² + daunorubicin&lt;br&gt;• *cytarabine 300 mg/m² + etoposide&lt;br&gt;• *cytarabine 300 mg/m² + teniposide&lt;br&gt;• *doxorubicin + ifosfamide&lt;br&gt;• doxorubicin + methotrexate 5 g/m²&lt;br&gt;• *etoposide + ifosfamide</td>
</tr>
</tbody>
</table>

* Pediatric evidence summarized in Table 4.
Note: An alphabetical listing of antineoplastic agents and the emetic risk is provided in Appendix E.

Level of Evidence: low and very low
Note: Level of evidence assigned by the authors of the source guideline to this recommendation was category 2B.

Grade of Recommendation: 1C
See Appendix C for key to levels of evidence and grades of recommendation.

Evidence

Table 3: Summary of Evidence Used to Inform Recommendation 5

<table>
<thead>
<tr>
<th>Studies</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holdsworth MR et al. 1995&lt;sup&gt;25&lt;/sup&gt;</td>
<td>• observational study&lt;br&gt;• nausea and vomiting assessed in 16 children (2 to 15 yrs) with acute lymphoblastic leukemia over 319 courses&lt;br&gt;• each course given with or without ondansetron at clinicians’ discretion&lt;br&gt;• 149 courses given with no antiemetic prophylaxis&lt;br&gt;• 9 patients received 100 courses of etoposide 150mg/m² + cytarabine 300 mg/m²&lt;br&gt;• no vomiting observed in 0/36 (0%) of etoposide 150 mg/m² + cytarabine 300 mg/m² courses without ondansetron and in 51/64 (80%) with ondansetron</td>
</tr>
<tr>
<td>Komada Y et al. 1999&lt;sup&gt;12&lt;/sup&gt;</td>
<td>• randomized study evaluating 2 doses of granisetron&lt;br&gt;• first of 3 identical antineoplastic courses given without AINV prophylaxis&lt;br&gt;• children (1 to 14 yrs) given methotrexate 3 g/m² + vincristine 1.5 mg/m²&lt;br&gt;• no vomiting observed in 26/74 (35%) of children receiving no prophylaxis</td>
</tr>
</tbody>
</table>
### Table 3: Summary of Evidence Used to Inform Recommendation 5 (continued)

<table>
<thead>
<tr>
<th>Studies where antiemetic prophylaxis was given:</th>
<th>Studies</th>
</tr>
</thead>
</table>
| **Dick et al. 1995**<sup>34</sup> | randomized parallel group study  
• 30 patients (1.5 to 15 yrs) randomized to receive either ondansetron or metoclopramide + dexamethasone during one antineoplastic course  
• patients received vincristine 1.5 mg/m² x 1 + daunorubicin 45 mg/m² daily x 2 + etoposide 100 mg/m² daily x 5 + cytarabine 100 mg/m² q12h x 10 + prednisolone 40 mg/m² daily x 7 + thioguanine 80 mg/m² daily x 5  
• on day 1 of antineoplastic therapy, no vomiting was observed in 3/15 (20%) of patients receiving metoclopramide + dexamethasone and 11/15 (73%) receiving ondansetron |
| **Holdsworth et al. 2006**<sup>2</sup> (supplementary data) | observational study  
• validated nausea/vomiting survey administered to 224 children over 1256 courses of antineoplastic therapy  
• ondansetron +/- dexamethasone given for AINV prophylaxis  
• complete response defined as no vomiting, retching or nausea  
• complete emetic control observed in < 80% of children given ondansetron as AINV prophylaxis and receiving: carboplatin 560 mg/m² + etoposide 100 mg/m² + vincristine 0.8-1.2 g/m² + doxorubicin 25-75 mg/m² ± etoposide 75-125 mg/m² + bleomycin (21 patients; 53 courses); cyclophosphamide > 1 g/m² ± etoposide 120 mg/m² (9 patients; 14 courses); cyclophosphamide 2.1 g/m² ± vincristine + doxorubicin 25 mg/m² or daunorubicin 1.25-1.5 mg/m² (13 patients; 60 courses); ifosfamide 1.8-3.4 mg/m² ± etoposide 100 mg/m² ± carboplatin 560 mg/m² (21 patients; 69 courses) |
| **Luisi FAV et al. 2006**<sup>35</sup> | randomized study comparing efficacy of granisetron vs metoclopramide + dimenhydrinate  
• 26 children (7 to 19 yrs) receiving 80 cycles of one of 3 antineoplastic regimens (epirubicin 75 mg/m² + ifosfamide 2.5 g/m²) or epirubicin 75 mg/m² + carboplatin 600 mg/m² or ifosfamide 2.5 g/m² + carboplatin 600 mg/m²  
• number of cycles of each antineoplastic regimen evaluated unknown  
• no vomiting, retching or nausea observed in 0% of cycles of dactinomycin 900 µg/m² + carboplatin 600 mg/m² cycles given metoclopramide and 7/11 (64%) of cycles given granisetron |
| **Miyajima Y et al. 1994**<sup>19</sup> | non-randomized cross-over study  
• 22 children receiving either 1 of 3 antineoplastic regimens on 2 consecutive cycles and randomized to receive either metoclopramide + promethazine or granisetron in cross-over design  
• no vomiting observed in 0% of cycles of dactinomycin 900 µg/m² + ifosfamide 3 g/m² given metoclopramide + promethazine prophylaxis |
| **Pinkerton CR et al. 1990**<sup>21</sup> | observational study  
• 30 children receiving one of 3 broad categories of antineoplastic regimens given ondansetron as prophylaxis before and during a single cycle (N=29) or 2 cycles with different antineoplastic regimens (N=1)  
• no vomiting observed on day 1 in 50% of courses of ifosfamide 6-9 g/m² ± doxorubicin 40-60 mg/m² cycles (5 patients) and ~60% of courses of cyclophosphamide 400-1000 mg/m² ± doxorubicin 40-60 mg/m² (8 patients) |
Table 3: Summary of Evidence Used to Inform Recommendation 5 (continued)

<table>
<thead>
<tr>
<th>Studies</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relling MV et al. 1993⁴⁶</td>
<td>• preliminary observational study: no vomiting observed in 1 of 58 antineoplastic courses (2%) in children receiving teniposide 200 mg/m² + cytarabine 300 mg/m² in first 8 hours despite administration of various antiemetics (e.g. phenothiazines, antihistamines)</td>
</tr>
<tr>
<td></td>
<td>• randomized comparison study of efficacy of chlorpromazine vs chlorpromazine + lorazepam in 25 children 1.7 – 7.5 yrs) receiving teniposide 200 mg/m² + cytarabine 300 mg/m²</td>
</tr>
<tr>
<td></td>
<td>• 3 or fewer vomits observed in the first 8 hours after initiation of antineoplastic therapy observed in 42/73 (58%) of courses</td>
</tr>
<tr>
<td>Sullivan MJ et al. 1992³⁷</td>
<td>• observational study</td>
</tr>
<tr>
<td></td>
<td>• 15 children (3 to 11 yrs) receiving numerous cycles of various antineoplastic combination regimens with ondansetron prophylaxis</td>
</tr>
<tr>
<td></td>
<td>• complete control of vomiting throughout entire study period (each day of active antineoplastic treatment and for 48 hrs following) observed in 6/12 (50%) cycles of cyclophosphamide 1 g/m² + cytarabine 150 mg/m²; 7/8 (88%) cycles of cyclophosphamide 600 mg/m² + vincristine 1.5 mg/m²; 1/2 (50%) cycles of cyclophosphamide 1 g/m² + doxorubicin 60 mg/m²; 4/4 (100%) cycles of cyclophosphamide 600 mg/m² + dactinomycin 1.5 mg/m²; 4/5 (80%) cycles of cyclophosphamide 300 mg/m² + cisplatin 100 mg/m²; 3/3 (100%) cycles of procarbazine 100 mg/m² + chlorambucil 6 mg/m²</td>
</tr>
</tbody>
</table>

**Discussion**

Pediatric experience confirms the recommendation of the source guideline to base the emetogenicity of a combination antineoplastic regimen on that of the agent of highest emetic risk for many combinations. In contrast, there are some reports of reduced emetogenicity of some combinations of antineoplastic relative to the emetogenicity of the combination’s most emetogenic single component. In these cases, the guideline development panel elected not to reduce the emetogenicity ranking of the combination below that of its most emetogenic single component since such an action is not intuitive and the evidence to support it is not robust.

The emetogenicity of the antineoplastic combinations listed in this recommendation appear to be more emetogenic than would have been appreciated by assessment of the agent of highest emetic risk when given as a single agent. It is consistent with the desire of the POGO AINV Guideline Development Panel to minimize break-through AINV to classify the emetogenicity these combinations higher than their most emetogenic single agent constituent. Hesketh et al developed a process for the evaluation of the emetogenicity of combination antineoplastic therapy in adults.⁵ With the exception of low-dose cytarabine which was not included in the Hesketh classification system, the antineoplastic combinations we have determined to be more emetogenic than their most emetogenic single constituent would also be ranked higher using the Hesketh system. The Hesketh system of evaluating the emetogenicity of antineoplastic combinations is no longer included in guidelines aimed at adult oncology patients. A more detailed assessment of the antineoplastic combinations listed in Table 3 using the Hesketh system was included in the version of this guideline that was sent to the expert reviewers. At the suggestion of the reviewers, it was deleted from the final version.

**Research Gaps**

Given that combination antineoplastic therapy is common in pediatric oncology practice, it is imperative that the emetogenicity of common combinations be investigated. It is likely that antiemetic prophylaxis may be inadequate for many children if selected based on the single antineoplastic agent of highest emetogenicity. Developers of treatment protocols involving combination antineoplastic therapy are urged to suggest antiemetic prophylaxis after review of this and the Hesketh classification systems.
QUESTION 3: IS THE RISK OF AINV WITH MULTIPLE DAY ANTINEOPLASTIC THERAPY REGIMENS DIFFERENT THAN THAT OF THE MOST EMETOGENIC ANTINEOPLASTIC THERAPY GIVEN ON ANY INDIVIDUAL DAY?

6. MULTIPLE DAY ANTINEOPLASTIC THERAPY

The emetogenicity of multiple day antineoplastic therapy is classified based on the emetic risk of the most highly emetogenic agent on each day of therapy.

Level of Evidence: very low
Note: Level of evidence assigned by the authors of the source guideline to this recommendation was category 2B.

Grade of Recommendation:
See Appendix B for key to levels of evidence and grades of recommendation.

Discussion
No pediatric experience was identified that was applicable to the determination of the risk of AINV with multiple day antineoplastic therapy. It is possible that patients may experience anticipatory, acute phase as well as delayed phase AINV by the end of a treatment cycle. In cases where AINV control deteriorates as a cycle progresses, clinicians may consider stepping up AINV prophylaxis and/or adding antiemetics aimed at controlling delayed phase AINV.

Research Gaps
AINV control over the course of multiple day antineoplastic therapy merits full exploration in order to determine the need for specific antiemetic strategies to enhance AINV control during the entire course. This is especially important in pediatric practice since multiple day antineoplastic therapy is very common.
EXTERNAL REVIEW AND CONSULTATION PROCESS

WHO WAS ASKED TO REVIEW THE GUIDELINE?
Content expert review: Physicians, nurses and pharmacists with an active clinical and/or research interest in antineoplastic-induced nausea and vomiting were asked to review the draft guideline. Content reviewers who submitted a review were: Ms. Christina Baggott, Dr. Yifan Rannan Eliya, Dr. Steven Grunberg, Dr. Anne Marie Langevin, Dr. Kathryn Mannix, Mr. Tom Oliver, Dr. Andrea Orsey, Dr. M.D. van der Wetering, Ms. Deborah Woods, Dr. Paul Hesketh, Ms. Rebecca Clark-Snow, Ms. Karin Jordan.

External stakeholder review: Physician, nurse and pharmacist members of POGO centres and their satellites, members of the C17 Standards and Guidelines Committee, physician, nurse and pharmacist members of C17 centres were asked to review the draft guideline.

WHAT PROCESS WAS FOLLOWED?
The willingness of potential content expert reviewers to review the guideline was determined by contacting them by telephone or e-mail. Once agreement was obtained, the draft guideline was sent both electronically and by courier along with instructions for the reviewer to complete a survey (Appendix F). Reviewers returned the completed survey by fax, mail or electronically.

The draft guideline was sent electronically to all those identified as stakeholder reviewers together with a survey (Appendix G). Stakeholder reviewers returned the completed survey by fax, mail or electronically.

DISCUSSION OF FEEDBACK
The survey results were discussed in detail by the POGO AINV Guideline Development Panel and a decision on each point was taken by consensus. When the decision of the panel was not unanimous, a revision was made if it was supported by at least 60% of the guideline development panel members.

Table 4: Specific Feedback from Content Expert Reviewers and Results of the Guideline Development Panel’s Discussion

<table>
<thead>
<tr>
<th>Expert Reviewer Comment</th>
<th>Panel Action / Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organize results according to health questions.</td>
<td>Done</td>
</tr>
<tr>
<td>Divide evidence tables into no Prophylaxis/prophylaxis.</td>
<td>Done</td>
</tr>
<tr>
<td>Methods: Insert brief summary of literature review in text.</td>
<td>Done</td>
</tr>
<tr>
<td>Results: guidelines reviewed 5 or 7?</td>
<td>Clarified. 6 guidelines were evaluated using AGREE. Only guidelines/citations that were not evaluated are now cited in the appendix.</td>
</tr>
<tr>
<td>Delete Hesketh from table or from entire guideline?</td>
<td>Hesketh classification was deleted from the table appearing with recommendation 5. Its inclusion in the text was retained.</td>
</tr>
<tr>
<td>I would not include oral agents that are administered over multiple days as the professed purpose of these guidelines is to define acute emetic risk and this is not really applicable to most oral agents.</td>
<td>The panel believed that emetogenicity of oral agents given in single or multiple days was not inherently different from that associated with IV or IT agents though concerns regarding the ability to administer an oral dose in its entirety may be more difficult in a vomiting child. Therefore, no change was made and oral agents were retained in the main table.</td>
</tr>
<tr>
<td>Statement on page 12 “at odds”.</td>
<td>This statement was deleted.</td>
</tr>
</tbody>
</table>
### Table 4: Specific Feedback from Content Expert Reviewers and Results of the Guideline Development Panel's Discussion (continued)

<table>
<thead>
<tr>
<th>Expert Reviewer Comment</th>
<th>Panel Action / Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>No compelling argument has been made to include carboplatin, thiotepa, dactinomycin or MTX &gt; 12 gm/m2 as highly emetogenic agents or to lower the cyclophosphamide dose threshold.</td>
<td>The panel believed that “upgrading” the emetogenicity classification of the agents listed was in keeping with the conservative approach and the desire to minimize the risk of breakthrough AINV as stated in the methods section. No change was made.</td>
</tr>
<tr>
<td>Many of the regimens that include an anthracycline and cyclophosphamide could be deleted by simply stating that an anthracycline + cyclophosphamide should be considered high risk.</td>
<td>Done</td>
</tr>
<tr>
<td>The weakness of this tool is that of its parent and lies in the moderately emetogenic category (30 to 90%). This will become even more apparent in the process of standardization of the antiemetic regimens for patients receiving agents listed in that category. This category is too broad…. For purpose of antiemetics recommendation, this category is not terribly discriminatory and will need to be broken down into moderately high and moderate categories.</td>
<td>The overly broad range of the moderately emetogenic category was included as a research gap in question 1 section 2.</td>
</tr>
<tr>
<td>On page 14 the description of the Holdsworth article is a bit unclear. Not all patients in the study were evaluated after their first course of chemotherapy.</td>
<td>Data regarding AINV experienced after first course of each agents listed was obtained from supplementary data provided by the authors. No change was made.</td>
</tr>
<tr>
<td>Delayed emesis day 8 written as up to 7 days post chemo, most definitions say; 24-120H post chemo which is up to 5 days.</td>
<td>NCCN guidelines state that delayed AINV may last up to 7 days after antineoplastic chemotherapy. No change was made.</td>
</tr>
<tr>
<td>Assessment of guidelines. 5 guidelines are mentioned, and one is used as a base for this guideline (NCCN). It would be nice to mention briefly the evidence of the other guidelines and the pediatric data available in these guidelines.</td>
<td>This information is available in the appendices.</td>
</tr>
<tr>
<td>On page 17 difficult to follow why carboplatin is based in the high emetogenic risk and most evidence is moderate emetogenic.</td>
<td>The conclusion of the Berrak study was changed to read “high-risk” rather than moderate-risk” emetogen.</td>
</tr>
<tr>
<td>Decreasing the dose from cyclo to 1.0gr/m2 in the high emetogenic risk is based on one study of Holdsworth and only looked at 21 patients. Be careful with this and rather although you mention it in the research gaps I would stress this even further.</td>
<td>Acknowledged</td>
</tr>
<tr>
<td>From page 31 onwards the authors try and classify the multiple agent antineoplastic therapy. Correctly they state that the highest emetogenic agent will dominate the antiemetic medication used. I find it extremely difficult to determine on base of extremely small studies to say if one or the other combination is high emetogenic or moderate. Authors refer to making use of the Hesketh classification system. One should stress in the text that this is deducted from adult literature and from 1997.</td>
<td>The Hesketh classification category has been removed from the data table. This was included only for reference not as a recommendation. The source of Hesketh’s system being adult data has been added to the discussion.</td>
</tr>
<tr>
<td>Should include ages 18-21?</td>
<td>Since this age group is well-served by the adult guidelines, no change has been made.</td>
</tr>
<tr>
<td>Under tools for application (page 37) suggests pre-printed and electronic order sets. Are there plans to develop standard ones as reference or examples?</td>
<td>No plans are being made to create these tools or templates.</td>
</tr>
<tr>
<td>Expert Reviewer Comment</td>
<td>Panel Action / Decision</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Is it possible to have a &quot;quick reference&quot; and an appendix that has the major classification areas all on one page for ease of use?</td>
<td>A quick reference has been prepared.</td>
</tr>
<tr>
<td>The background for the classification could be referred by page # as well.</td>
<td>Table of contents will provide this information.</td>
</tr>
<tr>
<td>You note on page 12 that published guidelines were not accepted if the guidelines were &quot;at odds with the clinical experience of group members.&quot; This immediately raises the question of whether opinions of members of POGO could override peer-reviewed evidence, also potentially limiting confidence in the evidence basis of your guidelines.</td>
<td>This phrase has been deleted since it does not reflect the workings of the panel. All decisions were based on evidence as outlined in the guideline text.</td>
</tr>
<tr>
<td>You have relied on the Hesketh algorithm (Ref 5) to establish emetogenic level for some of the combinations. However it should be noted that the Hesketh algorithm even as presented in the original manuscript was a proposal based on limited data that has never been prospectively validated. One weakness of this algorithm is that most complex regimens (as are commonly used in pediatric oncology) will have enough components adding to the total Hesketh level score that they will eventually be classified as Level 5.</td>
<td>The Hesketh ranking was added for comparison only and was not used to establish the rankings recommended. The Hesketh rankings have been deleted from the table and mention to it has been limited to the discussion.</td>
</tr>
<tr>
<td>Ranking combination regimens creates hazards based on the individual components as well. For example, cyclophosphamide plus doxorubicin is generally considered to be highly emetogenic. In your table, you list cyclophosphamide plus doxorubicin plus bleomycin as being highly emetogenic. Since bleomycin itself is only minimally emetogenic, this 3-drug classification adds very little to the 2-drug classification (that is, any combination that includes cyclophosphamide plus doxorubicin plus &quot;other&quot; will likely reach this level).</td>
<td>The bleomycin combination has been replaced by cyclophosphamide + doxorubicin.</td>
</tr>
<tr>
<td>Oral agents and multiple day chemotherapy raise similar problems. (Of note- most oral regimens do continue for multiple days). For such regimens, it is unclear whether the emetogenic ranking refers to the first day, the worst day, or a net impression of the entire course of treatment. Including oral agents and single-dose intravenous agents in the same emetogenicity table may confuse this distinction and cloud the meaning of your classifications.</td>
<td>The panel believed that emetogenicity of oral agents given in single or multiple days was not inherently different from that associated with IV or IT agents though concerns regarding the ability to administer an oral dose in its entirety may be more difficult in a vomiting child. Therefore, no change was made and oral agents were retained in the main table.</td>
</tr>
</tbody>
</table>
Information about the stakeholders, their specific feedback and results of the guideline development panel’s discussion of their comments are summarized in the tables below:

<table>
<thead>
<tr>
<th>Table 5: Institutions of Stakeholders Who Provided Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Canada</strong></td>
</tr>
<tr>
<td>Alberta Children’s Hospital,</td>
</tr>
<tr>
<td>Calgary, Alberta</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Janeway Child Health Centre,</td>
</tr>
<tr>
<td>St. John’s, Newfoundland</td>
</tr>
<tr>
<td>Stollery Children’s Hospital,</td>
</tr>
<tr>
<td>Edmonton, Alberta</td>
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<tr>
<td></td>
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<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Statement</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>The rationale for developing a guideline, as stated in the “Introduction” and “Scope and Purpose” sections of the draft guideline, is clear.</td>
</tr>
<tr>
<td>There is a need for a practice guideline on Emetogenicity Classification.</td>
</tr>
<tr>
<td>The literature search described in the guideline is relevant and complete.</td>
</tr>
<tr>
<td>The results of the studies described in the guideline are interpreted according to my understanding of the data.</td>
</tr>
<tr>
<td>The draft recommendations are clear.</td>
</tr>
<tr>
<td>I agree with the draft recommendations as stated.</td>
</tr>
<tr>
<td>This guideline should be approved by POGO</td>
</tr>
<tr>
<td>I would feel comfortable having these recommendations applied in my hospital.</td>
</tr>
</tbody>
</table>

*answered question: 29*

*skipped question: 0*
Table 7: Stakeholders’ opinion of likelihood of adoption of guideline in their practice.

<table>
<thead>
<tr>
<th>Response</th>
<th>Percent</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Likely</td>
<td>79.3%</td>
<td>23</td>
</tr>
<tr>
<td>Unsure</td>
<td>6.9%</td>
<td>2</td>
</tr>
<tr>
<td>Not at all likely</td>
<td>0.0%</td>
<td>0</td>
</tr>
<tr>
<td>Not applicable</td>
<td>13.8%</td>
<td>4</td>
</tr>
<tr>
<td>answered question</td>
<td></td>
<td>29</td>
</tr>
<tr>
<td>skipped question</td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

If this guideline is approved, how likely would you be to adopt these recommendations in your own practice?

Table 8: Additional Comments from Stakeholders and Response of Guideline Development Panel

<table>
<thead>
<tr>
<th>Stakeholder Comment</th>
<th>Panel Action / Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the Quick Summary AINV is not defined. In Table 1 under moderate level of emetic risk there should be a &quot;≥&quot; sign after methotrexate. Also in Table 1 the asterisk definition is missing from the bottom of the table (in both the summary and the document).</td>
<td>AINV defined on first use in text of Quick Summary. &quot;≥&quot; inserted in methotrexate entry in Table 1, moderate risk. The footnotes to Table 1 were added to the bottom of each page where table appears in the Quick Summary and document. Response not required.</td>
</tr>
<tr>
<td>A very impressive body of work. I would expect that this work is the first step in developing and disseminating treatment guidelines for AINV. I look forward to utilizing that guideline in practice. Well done.</td>
<td></td>
</tr>
<tr>
<td>I like the * to note peds evidence. I really like Table 2. We currently use the emetogenic potential for the most highly emetogenic agent for combination therapy, which for some combinations, underestimates antiemetic needs.</td>
<td>Response not required.</td>
</tr>
<tr>
<td>Procarbazine is placed in the highly emetogenic category. This oral agent is usually given in the outpatient setting for up to 7 days, along with prednisone. Based on the guidelines at our institution, prevention of AINV for highly emetogenic agents would require the use of high-dose dexamethasone, which is not the current practice for procarbazine. I do not see a comment on the support for the ranking of this agent.</td>
<td>Procarbazine is ranked as a high-risk emetogen by the source guideline and no published pediatric evidence was located to substantiate or refute this ranking. The use of dexamethasone as an antiemetic in children who are concurrently receiving corticosteroid agents for other indications will be addressed in future AINV management guidelines. Response not required.</td>
</tr>
<tr>
<td>The literature review was very thorough. The guideline is clear and complete for what its actual scope is defined as. However, I would have liked the scope of the guideline to include anticipatory and delayed nausea and vomiting, as it is a considerable issue in pediatric oncology. Also, the guideline would be more complete and practical for use across POGO centers if it also guided actual antiemetic therapy and dose selection.</td>
<td>These aspects of AINV are not within the scope of this guideline and will be addressed in planned future guidelines. Response not required.</td>
</tr>
</tbody>
</table>
### Table 8: Additional Comments from Stakeholders and Response of Guideline Development Panel (continued)

<table>
<thead>
<tr>
<th>Stakeholder Comment</th>
<th>Panel Action / Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>These recommendations provided evidence-based information on the emetogenicity of antineoplastic agents. These recommendations are valuable as we introduce newer agents whose emetogenic potential was unknown. They can be adapted and utilized for teaching purposes of new staff. Recommendations are already in place for standard meds.</td>
<td>Response not required.</td>
</tr>
<tr>
<td>Not a great amount of robust pediatric research to support the guidelines. Pre-printed orders would be advantageous and perhaps increase utilization of guidelines.</td>
<td>Response not required.</td>
</tr>
<tr>
<td>Our institution has a group practice and thus adaptation of the guideline will depend on consensus; though it is likely to be adopted because one of the authors is from our institution and so should be familiar with local practice.</td>
<td>Response not required.</td>
</tr>
<tr>
<td>I would use the document as a guideline for practice as I also have to work with our institutional guidelines and practice. If there were differences it would serve as a relevant document for suggesting any change in practice.</td>
<td>Response not required.</td>
</tr>
<tr>
<td>Evidence-based information supporting and expanding current practice is educational and research based. Emetic potential is part of orientation and chemotherapy approval process for the nursing staff. Evidence-based management guidelines would be beneficial. POGO would not need to approve these recommendations since they are evidence based supported by the literature but should support the recommendations and support development of management recommendations for practice.</td>
<td>Response not required.</td>
</tr>
<tr>
<td>The summary is clear and very readable which will translate to an easy tool to apply to patient care. While not familiar with all the agents specified in the recommendation, being at a satellite centre, I cannot comment on any gaps in the chemotherapeutic agents specified. Having gone through the brief study descriptions, the recommendations follow the evidence sited. Overall an extensive working document that in its summary would be easily applied. It might follow, if not already done, to do similar for the actual treatment of AINV among the various approaches.</td>
<td>Response not required.</td>
</tr>
<tr>
<td>Guidelines clear and complete with the caveats already noted with regard to the broadness of the moderate risk category. The lack of pediatric data is concerning. Will there be companion guideline matching effective anti-emetic therapy to antineoplastic agents?</td>
<td>Response not required.</td>
</tr>
<tr>
<td>A useful document, with substantial supportive data - this is, I think, a good first step that needs to be followed up with more specific guidelines for practical implementation.</td>
<td>Response not required.</td>
</tr>
<tr>
<td>Great work</td>
<td>Response not required.</td>
</tr>
</tbody>
</table>
PLAN FOR SCHEDULED REVIEW AND UPDATE

The POGO AINV Guideline Development Panel will review this guideline every 3 years and at any time if significant new information becomes available.

TOOLS FOR APPLICATION

The alphabetical emetogenicity classification chart of antineoplastic agents that appears in the summary may be used as a quick reference tool. Antiemetic agents chosen on the basis of the recommendations of this guideline are suggested to be included in pre-printed and electronic order sets for antineoplastic treatment of children developed by individual institutions.

IMPLEMENTATION CONSIDERATIONS

Users of this guideline are encouraged to incorporate the recommendations of the guideline into:

- antineoplastic treatment protocols and road maps;
- institutional guidelines for selection of antiemetic agents for the prevention of acute antineoplastic-induced nausea and vomiting;
- pre-printed or electronic (e.g. CPOE) order sets that include antineoplastic agents.

POTENTIAL ORGANIZATIONAL BARRIERS AND COST IMPLICATIONS

Organizational barriers to the acceptance and uptake of this guideline may include:

- dismissal of recommendations based on the relative scarcity of robust paediatric supporting evidence;
- reluctance by some clinicians to use state-of-the-art antiemetic agents including corticosteroid agents;
- lack of access to modern antiemetic agents. This will not be an issue in POGO centres and their satellites.

Costs related to antiemetic agents may increase as a result of this guideline. However, these costs are counter-balanced by potential reductions in admissions due to refractory AINV and/or dehydration following antineoplastic therapy and improvement in the quality of life experienced by pediatric cancer patients during treatment.

KEY REVIEW CRITERIA FOR MONITORING AND/OR AUDIT PURPOSES

Guideline acceptance and adherence may be monitored prospectively or retrospectively indirectly through audit of antiemetic selection.
REFERENCES


30. ESP Pharma. IV Busulfex (busulfan) injection product monograph; 2003.


ACKNOWLEDGEMENTS

The counsel of Ms. Carol Digout and Dr. Dorothy Barnard with respect to the AGREE and CAN-ADAPTE methodologies; the assistance of Ms. Elizabeth Uleryk, Director, Hospital Library, The Hospital for Sick Children with the literature and guideline searches; and the administrative assistance of Ms. Carla Bennett, Coordinator of Clinical Programs, Pediatric Oncology Group of Ontario are gratefully acknowledged.

PANEL MEMBERS

The guideline development panel was comprised of:

• L. Lee Dupuis, pediatric oncology pharmacist
• Sabrina Boodhan, pediatric pharmacist
• Lillian Sung, pediatric hematologist/oncologist
• Richard Hain, pediatric hematologist/oncologist
• Patricia McCarthy, pediatric oncology nurse practitioner
• Carol Portwine, pediatric hematologist/oncologist
• Mark Holdsworth, pediatric oncology pharmacist

THE GUIDELINE DEVELOPMENT PANEL MEMBERS HAD NO CONFLICTS OF INTEREST WITH RESPECT TO THE DEVELOPMENT OF THIS GUIDELINE. THE GUIDELINE WAS DEVELOPED INDEPENDENTLY FROM ANY FUNDING BODY OTHER THAN THOSE LISTED BELOW. ALL WORK PRODUCED BY THE POGO AINV GUIDELINE DEVELOPMENT PANEL IS EDITORIALLY INDEPENDENT OF ITS FUNDING AGENCIES.

FUNDING SOURCES

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Ministry of Health and Long Term Care, Ontario
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We welcome dialogue with anyone interested in any aspect of the program and respectfully ask that requests to copy or distribute any portions of this document be directed to Carla Bennett at the POGO office via e-mail (cbennett@pogo.ca) or by telephone (416-592-1232).
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1. GUIDELINE SEARCH

Search Strategy

The following processes were used to search for guidelines:

1. Review of scientific literature sources using empirical databases - Medline, Medline, Embase, Cumulative Index to Nursing & Allied Health Literature (CINHAL), Cochrane Systematic Review databases were systematically searched using the following search terms:
   - Medline Search Terms: nausea, vomiting, combined with terms antiemetics, antineoplastic agents, neoplasm, guideline or practice guideline, limited to “all child (0 to 18 years)”.
   - EMBASE Search Terms: nausea, vomiting, combined with terms antiemetics agents, antineoplastic agent, neoplasm, practice guideline, limited to child.
   - CINAHL Search Terms: nausea or vomiting, combined with terms antiemetics, antineoplastic agents, practice guidelines, limited to newborn or infant or child or adolescence.

2. Review of grey literature sources such as annual reports or publications of organizations as identified on the world-wide web - The internet search engine utilized was Google. Search terms included: antiemetics practice guidelines, nausea and vomiting guidelines paired with terms of children, and pediatric.

3. Review of local, provincial, national and international databases
   a. Professional oncology associations for antiemetics guidelines.
   b. International organizations or agencies or associations whose mandate is focused on systematic reviews or guideline development.

The organizations and agencies sites that were searched are included in Appendix B.

Inclusion / Exclusion Criteria

Inclusion:
1. Guidelines focused on clinical practice of practitioners relevant to pediatric antiemetics guidelines for pediatric hematology/oncology patients.
   a. Clinical practice guidelines: those specific to situations in which clinicians are making decisions about direct patient care.
   b. Best practice guidelines: those that identify the best choice from a range of appropriate health care options, as defined by a consensus of experts following review of relevant literature using systematic review methods.

2. Published between 1950-2008.

Exclusion*:
1. Guidelines for which it was not clear that the guideline statements or recommendations were based on a review of evidence from the literature and/or were not based on a source that used evidence to support the guideline development process

*Excluded guidelines may have still been considered by the panel during the guideline development process, but were not considered for the basis of guideline adaptation.
2. LITERATURE SEARCH

Search Strategies for Pediatric Oncology Group

**Database:** Ovid MEDLINE® <1950 to June Week 4 2008> plus Ovid AutoAlert Updates to November Week 3, 2009

**Sample Search Strategy:**

```
1 nauseas/ or vomiting/ (20916)
2 exp neoplasm/ (2001006)
3 1 and 2 (4539)
4 limit 3 to ("all child (0 to 18 years)" and (guideline or practice guideline)) (0)
5 limit 3 to (guideline or practice guideline) (6)
6 exp Antiemetics/ (112785)
7 exp Antineoplastic Agents/ (638008)
8 6 and 7 (44415)
9 limit 8 to ("all child (0 to 18 years)" and (guideline or practice guideline)) (2)
10 guidelines as topic/ or practice guidelines as topic/ (67267)
11 3 or 8 (48031)
12 10 and 11 (114)
13 limit 12 to "all child (0 to 18 years)" (19)
14 9 or 13 (20)
15 from 14 keep 1-20 (20)
```

**Database:** CINAHL - Cumulative Index to Nursing & Allied Health Literature <1982 to June Week 4 2008>

**Search Strategy:**

```
1 "nausea and vomiting"/ or nausea/ or vomiting/ (2723)
2 exp Neoplasms/ (89313)
3 1 and 2 (378)
4 exp Antiemetics/ (3594)
5 exp Antineoplastic Agents/ (17238)
6 4 and 5 (444)
7 3 or 6 (760)
8 limit 7 to (newborn infant <birth to 1 month> or infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescence <13 to 18 years>) (116)
9 limit 8 to practice guidelines (1)
10 Practice Guidelines/ (14769)
11 8 and 10 (2)
12 9 or 11 (2)
13 from 12 keep 1-2 (2)
```
**Database:** EMBASE <1980 to 2008 Week 26> plus Ovid AutoAlert Updates to 2009 Week 51

**Sample Search Strategy:**

<table>
<thead>
<tr>
<th>Number</th>
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<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&quot;nausea and vomiting&quot;/ or chemotherapy induced emesis/ or nausea/ or opioid induced emesis/ or radiation induced emesis/ or retching/ or vomiting/</td>
<td>107965</td>
</tr>
<tr>
<td>2</td>
<td>exp Neoplasm/</td>
<td>1429474</td>
</tr>
<tr>
<td>3</td>
<td>1 and 2</td>
<td>33653</td>
</tr>
<tr>
<td>4</td>
<td>exp Antiemetic Agent/</td>
<td>90027</td>
</tr>
<tr>
<td>5</td>
<td>exp Antineoplastic Agent/</td>
<td>695137</td>
</tr>
<tr>
<td>6</td>
<td>4 and 5</td>
<td>16370</td>
</tr>
<tr>
<td>7</td>
<td>3 or 6</td>
<td>45962</td>
</tr>
<tr>
<td>8</td>
<td>limit 7 to (infant &lt;to one year&gt; or child &lt;unspecified age&gt; or preschool child &lt;1 to 6 years&gt; or school child &lt;7 to 12 years&gt; or adolescent &lt;13 to 17 years&gt;)</td>
<td>3168</td>
</tr>
<tr>
<td>9</td>
<td>exp practice guideline/</td>
<td>137069</td>
</tr>
<tr>
<td>10</td>
<td>8 and 9</td>
<td>140</td>
</tr>
<tr>
<td>11</td>
<td>2 and 4 and 9</td>
<td>426</td>
</tr>
<tr>
<td>12</td>
<td>limit 11 to (infant &lt;to one year&gt; or child &lt;unspecified age&gt; or preschool child &lt;1 to 6 years&gt; or school child &lt;7 to 12 years&gt; or adolescent &lt;13 to 17 years&gt;)</td>
<td>34</td>
</tr>
<tr>
<td>13</td>
<td>3 and 4 and 9</td>
<td>245</td>
</tr>
<tr>
<td>14</td>
<td>limit 13 to (infant &lt;to one year&gt; or child &lt;unspecified age&gt; or preschool child &lt;1 to 6 years&gt; or school child &lt;7 to 12 years&gt; or adolescent &lt;13 to 17 years&gt;)</td>
<td>21</td>
</tr>
<tr>
<td>15</td>
<td>10 or 12 or 14</td>
<td>141</td>
</tr>
<tr>
<td>16</td>
<td>from 15 keep 1-141</td>
<td>141</td>
</tr>
</tbody>
</table>

**Database:** All EBM Reviews - Cochrane DSR, ACP Journal Club, DARE, CCTR, CMR, HTA, and NHSEED

**Search Strategy:**

<table>
<thead>
<tr>
<th>Number</th>
<th>Search Term</th>
<th>Count</th>
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</thead>
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<tr>
<td>1</td>
<td>(cancer: or neoplas: or oncolog:).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw]</td>
<td>49445</td>
</tr>
<tr>
<td>2</td>
<td>(nausea or nauseous or vomit: or emesis or &quot;anti-emetic:&quot; or &quot;anti emetic:&quot; or antiemetic:).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw]</td>
<td>16104</td>
</tr>
<tr>
<td>3</td>
<td>1 and 2</td>
<td>3246</td>
</tr>
<tr>
<td>4</td>
<td>(infan: or child: or teen: or adolescen: or (young adj2 adult:) or pediatric: or paediatric:).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw]</td>
<td>111019</td>
</tr>
<tr>
<td>5</td>
<td>3 and 4</td>
<td>436</td>
</tr>
<tr>
<td>6</td>
<td>from 5 keep 1-436</td>
<td>436</td>
</tr>
</tbody>
</table>

**Citations Reviewed and Excluded**


**Adult data; superseded by current MASCC guideline.**


**Not current; method of evidence assessment unclear.**


**Not a guideline**

Not a guideline


Not a guideline


Not a guideline


Not a guideline


Not a guideline

Gralla RJ, Roila F, Tonato M; Multinational Society of Supportive Care in Cancer; American Society of Clinical Oncology; Cancer Care Ontario; Clinical Oncological Society of Australia; European Oncology Nursing Society; European Society of Medical Oncology; National Comprehensive Cancer Network; Oncology Nursing Society; South African Society of Medical Oncology. The 2004 Perugia Antiemetic Consensus Guideline process: methods, procedures, and participants. Support Care Cancer 2005;13(2):77-9.

Adult data; superseded by current MASCC guideline


Adult data; incorporated into current MASCC guideline


Not a guideline; adult data


Not a guideline


Not a guideline


Not extensively referenced


Not a guideline


Adult data; superseded by current MASCC guideline
3. LITERATURE SEARCH – EMETOCGENIC POTENTIAL OF ANTINEOPLASTIC AGENTS IN CHILDREN

Search Strategy

The following processes were used to search for literature on the emetogenic potential of antineoplastic agents in children:

1. **Review of scientific literature sources using empirical databases** - Medline, Embase, Cumulative Index to Nursing & Allied Health Literature (CINHAL), Cochrane Systematic Review databases were systematically searched using the following search terms:
   - Medline Search Terms: nausea, vomiting, combined with terms antineoplastic agents, neoplasm, classification, limited to “all child (0 to 18 years)”.
   - EMBASE Search Terms: nausea, vomiting, combined with terms cancer chemotherapy, antineoplastic agent, antineoplastic activity, limited to child.

2. **Review of grey literature sources such as annual reports or publications of organizations as identified on the world-wide web** - The internet search engine utilized was Google. Search terms included: emetogenic potential, emetogenicity, cancer, antineoplastic agent, chemotherapy, nausea and vomiting guidelines paired with terms of children, and pediatric.

3. **Review of local, provincial, national and international databases**
   - Professional oncology associations for antiemetics guidelines.
   - International organizations or agencies or associations whose mandate is focused on systematic reviews or guideline development.

The organizations and agencies sites that were searched are included in Appendix B.

Sources of Evidence

- References from guidelines found in Web of Sciences for citations

- Searches of Medline, Embase, CINAHL, CDSR (Cochrane Database of Systematic Reviews), DARE (Database of Abstracts of Reviews of Effects), in July 2008 for documents providing data on emetogenic potential of antineoplastic agents in children

Inclusion Criteria

- The population of interest was: children and youth (age up to 18 years) with cancer

Exclusion Criteria

- Articles where evidence was not provided were excluded
Citations Reviewed and Excluded


   Review; extrapolated from adult data


   Review; expert opinion


   Not applicable


   Not applicable


   Review


   Review


   Not extensively referenced; institution specific protocol


   Review article; adult data


   Adult data


   Review article; extrapolated from adult data

Mertens WC, Higby DJ, Brown D, Parisi R, Fitzgerald J, Benjamin EM, Lindenauer PK. Improving the care of patients with regard to chemotherapy-induced nausea and emesis: the effect of feedback to clinicians on adherence to antiemetic prescribing guidelines.

   Adult data


   Adult data


   Review; expert opinion


   Not applicable

Not applicable


Expert opinion

4. LITERATURE SEARCH: AMSACRINE-INDUCED NAUSEA AND VOMITING IN CHILDREN

Ovid MEDLINE(R) 1950 to Present with Daily Update

<table>
<thead>
<tr>
<th>exp Amsacrine/</th>
<th>1099</th>
</tr>
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<tbody>
<tr>
<td>limit 1 to (&quot;all infant (birth to 23 months)&quot; or &quot;all child (0 to 18 years)&quot; or &quot;newborn infant (birth to 1 month)&quot; or &quot;infant (1 to 23 months)&quot; or &quot;preschool child (2 to 5 years)&quot; or &quot;child (6 to 12 years)&quot; or &quot;adolescent (13 to 18 years)&quot;)</td>
<td>164</td>
</tr>
<tr>
<td>exp vomiting/ or exp antiemetics/</td>
<td>130661</td>
</tr>
<tr>
<td>3 and 2</td>
<td>8</td>
</tr>
</tbody>
</table>


Adult data


Not applicable


Not applicable


Adult data; not applicable


Adult data


Adult data


**Adult data**

**EMBASE 1980 to 2009 Week 30**

<table>
<thead>
<tr>
<th>exp amsacrine/ or exp amsacrine derivative/</th>
<th>3147</th>
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</thead>
<tbody>
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<td>limit 1 to (infant &lt;to one year&gt; or child &lt;unspeced age&gt; or preschool child &lt;1 to 6 years&gt; or school child &lt;7 to 12 years&gt; or adolescent &lt;13 to 17 years&gt;)</td>
<td>374</td>
</tr>
<tr>
<td>exp &quot;nausea and vomiting&quot;/ or exp vomiting/</td>
<td>121998</td>
</tr>
<tr>
<td>exp antiemetic agent/</td>
<td>94315</td>
</tr>
<tr>
<td>3 and 2</td>
<td>32</td>
</tr>
<tr>
<td>4 and 2</td>
<td>12</td>
</tr>
<tr>
<td>6 or 5</td>
<td>34</td>
</tr>
</tbody>
</table>


**Not applicable**


**Adult data**


**Not applicable**


**Adult data**


**Not applicable**


**Not applicable**


**Review article**


**Results not reported per individual antineoplastic agents**

Not applicable; not extensively referenced


Specific details not reported


Review article


Review article


Not applicable


Not applicable


Not applicable

5. LITERATURE SEARCH: BUSULFAN-INDUCED NAUSEA AND VOMITING IN CHILDREN

Ovid MEDLINE(R) 1950 to Present with Daily Update

<table>
<thead>
<tr>
<th>Search Query</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Busulfan/</td>
<td>3301</td>
</tr>
<tr>
<td>limit 1 to (&quot;all infant (birth to 23 months)&quot; or &quot;all child (0 to 18 years)&quot; or &quot;newborn infant (birth to 1 month)&quot; or &quot;infant (1 to 23 months)&quot; or &quot;preschool child (2 to 5 years)&quot; or &quot;child (6 to 12 years)&quot; or &quot;adolescent (13 to 18 years)&quot;)</td>
<td>850</td>
</tr>
<tr>
<td>exp Vomiting/</td>
<td>21339</td>
</tr>
<tr>
<td>3 and 2</td>
<td>2</td>
</tr>
</tbody>
</table>


Pediatric data combined with adult data


Article not in English/French (Japanese)
EMBASE 1980 to 2009 Week 31

| exp busulfan/ae, to [Adverse Drug Reaction, Drug Toxicity] | 2135 |
| limit 1 to (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years>) | 380 |
| exp "nausea and vomiting"/ or exp vomiting/ | 141582 |
| 3 and 2 | 38 |


No incidence data provided


Pediatric data combined with adult data


Not applicable


Not specific to busulfan

McTiernan A, Driver D, Michelagnoli MP, Kilby AM, Whelan JS. High dose chemotherapy with bone marrow or peripheral stem cell rescue is an effective treatment option for patients with relapsed or progressive Ewing's sarcoma family of tumours. Annals of Oncology. 2006;17(8):1301-1305.

Not specific to busulfan


Not applicable


Review article


Not applicable


Not applicable


Specific details not reported

**Incidences of diarrhea and vomiting grouped together**


**Specific details not reported**


**Not applicable**


**Not applicable**


**Not applicable**


**Not applicable**


**Not applicable**


**Pediatric data grouped with adult data**


**Time course of vomiting observed unknown**


**Not applicable**


**Not applicable**

Not applicable


Not applicable


Not applicable


Not applicable


Not applicable


Not applicable


Incidence of nausea and vomiting grouped with diarrhea


Incidence of nausea and vomiting grouped with diarrhea - excluded


Not applicable


Not applicable


Not applicable


Review article


Previously reviewed

**Review article**

Vaughan WP, Dennison JD, Reed EC, Klassen L, McGuire TR, Sanger WG, Kumar PP, Warkentin PI, Gordon BG, Bierman PJ, Coccia PF, Armitage JO. Improved results of allogeneic bone marrow transplantation for advanced hematologic malignancy using busulfan, cyclophosphamide and etoposide as cytoreductive and immunosuppressive therapy. Bone Marrow Transplantation. 1991;8(6):489-495.

**Pediatric data grouped with adult data; not applicable**


**Not applicable; review article; adult data**

6. **LITERATURE SEARCH: CLOFARABINE-INDUCED NAUSEA AND VOMITING IN CHILDREN**

**Ovid MEDLINE(R) 1950 to Present with Daily Update**

<table>
<thead>
<tr>
<th>clofarabine.tw.</th>
<th>101</th>
</tr>
</thead>
<tbody>
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<td>limit 1 to (&quot;all infant (birth to 23 months)&quot; or &quot;all child (0 to 18 years)&quot; or &quot;newborn infant (birth to 1 month)&quot; or &quot;infant (1 to 23 months)&quot; or &quot;preschool child (2 to 5 years)&quot; or &quot;child (6 to 12 years)&quot; or &quot;adolescent (13 to 18 years)&quot;&quot;)</td>
<td>22</td>
</tr>
<tr>
<td>exp vomiting/ or exp antiemetics/</td>
<td>130679</td>
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<td>3 and 2</td>
<td>1</td>
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</table>


**Not applicable**

**EMBASE 1980 to 2009 Week 51**

<table>
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<tr>
<th>exp clofarabine/</th>
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<td>limit 1 to (infant &lt;to one year&gt; or child &lt;unspecified age&gt; or preschool child &lt;1 to 6 years&gt; or school child &lt;7 to 12 years&gt; or adolescent &lt;13 to 17 years&gt;)</td>
<td>40</td>
</tr>
<tr>
<td>exp &quot;nausea and vomiting&quot;/ or exp vomiting/</td>
<td>127397</td>
</tr>
<tr>
<td>exp antiemetic agent/</td>
<td>96160</td>
</tr>
<tr>
<td>3 and 2</td>
<td>8</td>
</tr>
<tr>
<td>4 and 2</td>
<td>0</td>
</tr>
<tr>
<td>6 or 5</td>
<td>8</td>
</tr>
</tbody>
</table>


**Specific details not reported**


**Not applicable**


**Not applicable**

**Not applicable**


**Specific details not reported**


**Specific details not reported**

7. **LITERATURE SEARCH: THIOTEPA-INDUCED NAUSEA AND VOMITING IN CHILDREN**

Ovid MEDLINE(R) 1950 to Present with Daily Update

| exp Thiotepa/ | 2385 |
| limit 1 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)") | 243 |
| exp Vomiting/ | 21339 |
| 3 and 2 | 1 |


*Article not in English/French (Russian)*

EMBASE

| exp Thiotepa/ | 7716 |
| limit 1 to (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>) | 976 |
| exp "nausea and vomiting"/ or exp vomiting/ | 141394 |
| 3 and 2 | 56 |


**Specific details not reported**


**Adult data**


**Adolescent and adult data**

**Not applicable**


**Not applicable**


**Review article**


**Adult data**


**Not applicable**


**Not applicable**


**Adolescent and adult data**


**Not specific to thiotepa; nausea and vomiting grouped with other side effects**


**Adult data**


**Not specific to thiotepa**


**Not applicable**

Not applicable


Not applicable


Review article


Not applicable


Not applicable


Adolescent and adult data


Not applicable


Not applicable


Specific details not reported


Adult data


Not applicable

**Adult data**


**Adolescent and adult data**


**Specific details not reported**


**Adult data**


**Not applicable**


**Not applicable**


**Not applicable**


**Specific details not reported**


**Specific details not reported**


**Specific details not reported**

Specific details not reported


Not applicable


Adult data


Specific details not reported


Not applicable


Not applicable


Incidence of nausea and vomiting was grouped with incidence of diarrhea

Incidence of nausea and vomiting was grouped with incidence of diarrhea


Pediatric data combined with adult data


Incidence of nausea and vomiting was grouped with incidence of diarrhea


Specific details not reported

Incidence of nausea and vomiting was grouped with incidence of diarrhea


Specific details not reported


Specific details not provided

**Review**


**Not applicable**


**Specific details not reported**


**Specific details not reported**


**Adolescent and adult data**

8. **LITERATURE SEARCH: ETOPOSIDE-INDUCED NAUSEA AND VOMITING IN CHILDREN**

**Ovid MEDLINE(R) 1950 to September Week 2 2009**

<table>
<thead>
<tr>
<th>Search Term</th>
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<tr>
<td>exp Etoposide/</td>
<td>12495</td>
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<td>2588</td>
</tr>
<tr>
<td>exp Vomiting/</td>
<td>21430</td>
</tr>
<tr>
<td>3 and 2</td>
<td>14</td>
</tr>
</tbody>
</table>


**Adolescent and adult data**


**Not applicable**


**Not applicable**


**Not applicable**

Not applicable


Adolescent and adult data


Not applicable


Article not in English/French (Japanese)


Adolescent and adult data


Adolescent and adult data


Adolescent and adult data


Pediatric and adult data combined

EMBASE

| exp etoposide/ae, to [Adverse Drug Reaction, Drug Toxicity] | 8724 |
| exp etoposide/iv, ia [Intravenous Drug Administration, Intraarterial Drug Administration] | 2162 |
| 1 and 2 | 993 |
| exp etoposide derivative/to, ae [Drug Toxicity, Adverse Drug Reaction] | 13 |
| exp etoposide derivative/iv [Intravenous Drug Administration] | 2 |
| 4 and 5 | 0 |
| limit 3 to (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years>) | 132 |
| exp "nausea and vomiting"/ or exp vomiting/ | 141582 |
| 8 and 7 | 29 |

Specific details not reported


Specific details not reported

Li B, Yang JL, Shi YK, He XH, Han XH, Zhou SY, Liu P, Yang S, Zhang CG. Etoposide 1.0 g/m2 or 1.5 g/m2 combined with granulocyte colony-stimulating factor for mobilization of peripheral blood stem cells in patients with malignancy: Efficacy and toxicity. Cytotherapy. 2009;11(3):362-371.

Adolescent and adult data


Specific details not reported


Specific details not reported


Review article


Not applicable


Not applicable


Pediatric and adult data combined


Not applicable


Specific details not reported

Specific details not reported


Specific details not reported


Adolescent and adult data


Specific details not reported


Grouped anorexia data with vomiting


Adolescent and adult data


Grouped diarrhea data with vomiting


Review article


Pediatric and adult data combined


Specific details not reported


Pediatric and adult data combined

Not applicable


Specific details not reported


Specific details not reported


Specific details not reported

9. LITERATURE SEARCH: MELPHALAN-INDUCED NAUSEA AND VOMITING IN CHILDREN

Ovid MEDLINE(R) 1950 to September Week 2 2009

| exp Melphalan/                              | 5852 |
| limit 1 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)") | 639  |
| exp Vomiting/                               | 21430|
| 3 and 2                                     | 7    |


Not applicable


Adult data


Specific details not reported


Article not in English/French (Japanese)


Adult data
**Article not in English/French (Russian)**

**Not applicable**

**EMBASE**

| exp melphalan/ | 19636 |
| limit 1 to (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>) | 2122 |
| exp "nausea and vomiting"/ or exp vomiting/ | 141394 |
| 3 and 2 | 108 |
| limit 4 to (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years>) | 58 |
| exp melphalan/ae, to [Adverse Drug Reaction, Drug Toxicity] | 27 |

**Not applicable**

**Not applicable**

**Not applicable**

**Not applicable**

**Not applicable**

McTiernan A, Driver D, Michelagnoli MP, Kilby AM, Whelan JS. High dose chemotherapy with bone marrow or peripheral stem cell rescue is an effective treatment option for patients with relapsed or progressive Ewing's sarcoma family of tumours. Annals of Oncology. 2006;17(8):1301-1305.  
**Not applicable**

**Review article**

POGO Emetogenicity Classification Guidelines

Not applicable


Not applicable


Specific details not reported


Not applicable


Not applicable


Specific details not reported


Not applicable


Not applicable; specific details not reported


Not applicable


Not applicable


Not applicable; not extensively referenced


Not applicable

Specific details not reported


Not applicable


Not applicable


Not applicable


Not applicable


Not applicable


Not applicable


Review article

10. LITERATURE SEARCH: MERCaptopurine-INDUCED NAUSEA AND VOMITING IN CHILDREN

Ovid MEDLINE(R) 1950 to September Week 2 2009

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<td>3899</td>
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<td>21430</td>
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<td>3 and 2</td>
<td>13</td>
</tr>
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</table>


Article not in English/French (Portuguese)


Not applicable

Specific details not reported


Not applicable


Not applicable


Specific details not reported


Adult data


Not applicable


Article not in English/French (German)


Article not in English/French (Italian)


Adult data


Not applicable


Not applicable
EMBASE

| exp mercaptopurine/ae, to [Adverse Drug Reaction, Drug Toxicity] | 1932 |
| limit to (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years>) | 393 |
| exp "nausea and vomiting"/ or exp vomiting/ | 141582 |
| 3 and 2 | 43 |
| exp Crohn disease/ | 28970 |
| exp irritable colon/ | 7868 |
| 6 or 5 | 36398 |
| 4 not 7 | 33 |
| exp ulcerative colitis/ | 25439 |
| 7 or 9 | 51440 |
| 4 not 10 | 33 |


Specific details not reported


Specific details not reported


Not applicable; not specific to mercaptopurine


Not applicable


Not applicable


Specific details not reported


Not applicable


Review article


Specific details not reported
  Not applicable

  Not applicable

  Specific details not reported

  Previously reviewed; specific details not reported

  Not applicable

  Not applicable

  Not applicable

  Not applicable

  Not applicable

  Specific details not reported

  Not applicable

  Previously reviewed; specific details not reported

  Not applicable

Specific details not reported


Specific details not reported


Not applicable


Review article


Not applicable


Review article


Pediatric data grouped with adult data


Article not in English (Japanese)

11. LITERATURE SEARCH: TENIPOSIDE-INDUCED NAUSEA AND VOMITING IN CHILDREN

Ovid MEDLINE(R) 1950 to September Week 2 2009

| exp Teniposide/ | 946 |
| limit 1 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)") | 206 |
| exp Vomiting/ | 21430 |
| 3 and 2 | 2 |

EMBASE

| exp Teniposide/ | 4548 |
| limit 1 to (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>) | 856 |
| exp "nausea and vomiting"/ or exp vomiting/ | 141394 |
| 3 and 2 | 38 |

Not applicable


Not applicable


Not applicable


Not applicable


Not applicable


Not applicable


Specific details not reported


Not applicable


Not applicable


Not applicable


Specific details not reported


Not applicable


Adult data

*Article not in English/French (Spanish)*


*Not applicable*


*Specific details not reported*


*Not specific to teniposide*


*Specific details not reported*


*Specific details not reported*


*Specific details not reported*


*Not applicable*


*Not applicable*


*Review article*


*Not applicable*


*Review article; not applicable*

Specific details not reported


Article not in English (German)


Data not specific to teniposide


Adolescent and adult data


Specific details not reported


Not applicable


The three patients reported to have experienced nausea/vomiting did not receive teniposide


Adolescent data


Not applicable


Review article


Specific details not reported


Not applicable


Not applicable


Not applicable
12. LITERATURE SEARCH: VINDESINE-INDUCED NAUSEA AND VOMITING IN CHILDREN

Ovid MEDLINE(R) 1950 to Present with Daily Update

<table>
<thead>
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<td>exp Vomiting/</td>
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<tr>
<td>3 and 2</td>
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**Adult data**


**Adolescent and adult data**

EMBASE 1980 to 2009 Week 31

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<td>330</td>
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<td>exp &quot;nausea and vomiting&quot;/ or exp vomiting/</td>
<td>122213</td>
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</table>


**Adult data**


**Adolescent and adult data**


**Adolescent and adult data**

Adolescent and adult data


Not applicable


Not applicable


Not applicable


Adult data


Adult data


Adolescent and adult data


Not applicable


Not applicable


Not applicable

**Adolescent and adult data**


Not applicable


Review article; not applicable


**Adult data**


**Adolescent and adult data**


Not applicable


**Adolescent and adult data**


**Adolescent and adult data**


**Adolescent and adult data**


**Adult data; not applicable**


**Not specific to vindesine**


Previously reviewed; not applicable

**Not specific to vindesine**


**Adult data**


**Article not in English/French**


**Adult data**


**Adult data**


**Specific details not reported**


**Specific details not reported**

13. **LITERATURE SEARCH: PEGASPARGASE-INDUCED NAUSEA AND VOMITING IN CHILDREN**

Ovid MEDLINE(R) 1950 to September Week 2 2009

<table>
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<tr>
<th>exp Asparaginase/</th>
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<td>33454</td>
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<tr>
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<td>136</td>
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<td>limit 3 to (&quot;all infant (birth to 23 months)&quot; or &quot;all child (0 to 18 years)&quot; or &quot;newborn infant (birth to 1 month)&quot; or &quot;infant (1 to 23 months)&quot; or &quot;preschool child (2 to 5 years)&quot; or &quot;child (6 to 12 years)&quot; or &quot;adolescent (13 to 18 years)&quot;)</td>
<td>63</td>
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<td>exp Vomiting/</td>
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<td>4 and 5</td>
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EMBASE 1980 to 2009 Week 43

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<td>80</td>
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<tr>
<td>exp &quot;nausea and vomiting&quot;/ or exp vomiting/</td>
<td>125292</td>
</tr>
<tr>
<td>3 and 2</td>
<td>7</td>
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</tbody>
</table>

   Not applicable

   Adolescent and adult data

   Not applicable; review

   Not applicable

   Not applicable

   Review article

   Review article
APPENDIX B: WEBSITES SEARCHED FOR GUIDELINES AND STANDARDS

WEBSITES SEARCHED

**CANADIAN CANCER ACADEMIC CENTERS**
Alberta Cancer Board: [www.cancerboard.ab.ca](http://www.cancerboard.ab.ca)
British Columbia Cancer Agency: [www.bc.cancer.ca](http://www.bc.cancer.ca)
Cancer Care Ontario Practice Guideline Initiative
Saskatchewan Cancer Agency: [www.scf.sk.ca](http://www.scf.sk.ca)

**INTERNATIONAL CANCER ACADEMIC CENTERS**
American Society of Clinical Oncology
American Cancer Society
Children's Hospital of Philadelphia: [www.chop.edu/consumer/index.jsp](http://www.chop.edu/consumer/index.jsp)
International Oncology Network
Monroe Carell Jr’s Children’s Hospital of Vanderbilt: [www.vanderbiltchildrens.com](http://www.vanderbiltchildrens.com)
St. Jude’s Children's: [www.stjude.org](http://www.stjude.org)*

**PROFESSIONAL ASSOCIATIONS AND AGENCIES**
Agency for Quality in Medicine (German, guidelines in English)
American Society of Clinical Oncology: [www.asco.org](http://www.asco.org)
Association of Pediatric Hematology/Oncology Nurses: [www.apon.org](http://www.apon.org)
Canadian Agency for Drugs and Technology in Health
Children’s Oncology Group: [www.childrensoncologygroup.org](http://www.childrensoncologygroup.org)
Food and Drug Administration
Registered Nurses Association of Ontario (RNAO): [www.rano.org](http://www.rano.org)
Associations of Community Cancer Centres: [www.accc-cancer.org](http://www.accc-cancer.org)*
International Society of Pediatric Oncology: [www.siop.nl](http://www.siop.nl)*
Institute for Clinical Systems Improvement

**ACADEMIC AND GOVERNMENT ASSOCIATED WEBSITES**
SIGN: [www.sign.ac.uk](http://www.sign.ac.uk)
National Institute for Health and Clinical Excellence: [www.nice.org.uk](http://www.nice.org.uk) (guidance.nice.org.uk)

**CANCER RESOURCE WEBSITES**
Cancer Backup (UK)
Cancer Index: [www.cancerindex.org](http://www.cancerindex.org)
National Comprehensive Cancer Network (NCCN)

**GUIDELINE SPECIFIC WEBSITES**
Cochrane Collaboration
National Institute for Clinical Evidence (NICE)
National Library for Health Care (NHS)
National Quality Measures Clearinghouse
New Zealand Guidelines Group
Ontario Guidelines Advisory Committee (GAC) Recommended Clinical Practice Guidelines
Scottish Intercollegiate Guideline Network (SIGN)
### APPENDIX C: AGREE SCORES OF GUIDELINES REVIEWED FOR ADAPTATION


| Question | 1 | 2 | 3 | Scope & Purpose Score | 4 | 5 | 6 | 7 | Stakeholder Involvement Score | 8 | 9 | 10 | 11 | 12 | 13 | 14 | Rigor Score | 15 | 16 | 17 | 18 | Clarity & Presentation Score | 19 | 20 | 21 | Applicability Score | 22 | 23 | Editorial Independence Score |
| Rater#1  | 4 | 3 | 3 | 10                      | 3 | 1 | 3 | 1 | 8                              | 3 | 3 | 2 | 1 | 3 | 3 | 1 | 16                     | 4 | 4 | 4 | 1 | 9                    | 1 | 1 | 1 | 1 | 3                    | 2 | 2 | 1                        |
| Rater#2  | 4 | 4 | 4 | 12                      | 2 | 1 | 4 | 2 | 9                              | 4 | 3 | 3 | 3 | 1 | 2 | 19                     | 3 | 4 | 4 | 4 | 11                   | 1 | 1 | 1 | 1 | 3                    | 2 | 1 | 3                        |
| Rater#5  | 4 | 4 | 3 | 11                      | 3 | 1 | 1 | 5 | 4                              | 4 | 3 | 4 | 3 | 1 | 1 | 20                     | 4 | 1 | 3 | 4 | 12                    | 1 | 1 | 1 | 1 | 3                    | 2 | 1 | 3                        |
| Rater#6  | 4 | 4 | 4 | 12                      | 1 | 1 | 1 | 7 | 2                              | 2 | 2 | 1 | 3 | 1 | 1 | 13                     | 4 | 2 | 4 | 4 | 14                    | 1 | 1 | 1 | 3 | 3                    | 1 | 4 | 5                        |
| Rater#7  | 4 | 4 | 2 | 10                      | 1 | 1 | 1 | 4 | 2                              | 2 | 1 | 3 | 1 | 3 | 1 | 12                     | 4 | 1 | 3 | 2 | 10                    | 1 | 1 | 1 | 3 | 1                    | 1 | 1 | 3                        |

- Obtained Score: 55
- Minimal Score: 15
- Maximum Score: 140
- Obtained-Minimal: 40
- Maximum-Minimal: 105

**Standardized Domain Scores**: 89


| Question | 1 | 2 | 3 | Scope & Purpose Score | 4 | 5 | 6 | 7 | Stakeholder Involvement Score | 8 | 9 | 10 | 11 | 12 | 13 | 14 | Rigor Score | 15 | 16 | 17 | 18 | Clarity & Presentation Score | 19 | 20 | 21 | Applicability Score | 22 | 23 | Editorial Independence Score |
| Rater#1  | 4 | 3 | 3 | 10                      | 3 | 1 | 1 | 1 | 6                              | 4 | 3 | 2 | 3 | 4 | 1 | 19                     | 4 | 4 | 4 | 2 | 10                    | 1 | 1 | 1 | 1 | 3                    | 1 | 1 | 1                        |
| Rater#2  | 4 | 4 | 2 | 10                      | 3 | 1 | 1 | 1 | 6                              | 4 | 3 | 2 | 2 | 2 | 4 | 21                     | 3 | 4 | 4 | 4 | 11                    | 2 | 1 | 3 | 3 | 6                    | 4 | 4 | 5                        |
| Rater#6  | 4 | 4 | 4 | 12                      | 4 | 1 | 4 | 1 | 10                             | 4 | 4 | 4 | 3 | 4 | 4 | 27                     | 4 | 4 | 4 | 4 | 16                    | 2 | 2 | 3 | 7 | 4                    | 4 | 8 | 7                        |
| Rater#7  | 4 | 2 | 2 | 8                       | 2 | 1 | 2 | 1 | 6                              | 4 | 4 | 4 | 3 | 3 | 1 | 22                     | 4 | 4 | 3 | 1 | 12                    | 1 | 2 | 1 | 4 | 4                    | 4 | 5 | 4                        |

- Obtained Score: 40
- Minimal Score: 12
- Maximum Score: 112
- Obtained-Minimal: 28
- Maximum-Minimal: 36

**Standardized Domain Scores**: 78

POGO Emetogenicity Classification Guidelines

| Question | 1 | 2 | 3 | Scope & Purpose Score | 4 | 5 | 6 | 7 | Stakeholder Involvement Score | 8 | 9 | 10 | 11 | 12 | 13 | 14 | Rigor Score | 15 | 16 | 17 | 18 | Clarity & Presentation Score | 19 | 20 | 21 | Applicability Score | 22 | 23 | Editorial Independence Score |
|----------|---|---|---|------------------------|---|---|---|---|-------------------------------|---|---|---|---|---|---|---|--------------|---|---|---|--------------|---|---|------------------------|
| Rater#2  | 4 | 4 | 1 | 9                      | 4 | 2 | 1 | 3 | 3 | 3 | 4 | 20 | 3 | 1 | 4 | 4 | 12 | 1 | 1 | 2 | 4 | 1 | 1 | 2 |
| Rater#3  | 3 | 3 | 3 | 3                      | 8 | 3 | 3 | 3 | 3 | 3 | 3 | 19 | 3 | 2 | 3 | 2 | 10 | 2 | 2 | 2 | 6 | 2 | 1 | 3 |
| Rater#4  | 4 | 3 | 2 | 3                      | 7 | 2 | 2 | 1 | 5 | 1 | 1 | 1 | 2 | 3 | 1 | 9 | 2 | 1 | 3 | 1 | 7 | 1 | 3 | 1 | 5 | 1 | 1 | 2 |
| Rater#5  | 4 | 3 | 1 | 1                      | 11 | 4 | 4 | 4 | 4 | 4 | 3 | 4 | 27 | 4 | 4 | 4 | 4 | 16 | 4 | 2 | 1 | 7 | 1 | 1 | 2 |
| Rater#7  | 2 | 2 | 2 | 6                      | 4 | 1 | 2 | 1 | 3 | 2 | 2 | 3 | 2 | 4 | 19 | 3 | 3 | 2 | 2 | 10 | 3 | 1 | 3 | 7 | 3 | 1 | 1 |

Maximum Obtained Score: 94
Minimum Score: 15
Maximum Score: 60
Obtained-Minimal: 26
Minimum-Minimal: 45

Standardized Domain Scores: 58


| Question | 1 | 2 | 3 | Scope & Purpose Score | 4 | 5 | 6 | 7 | Stakeholder Involvement Score | 8 | 9 | 10 | 11 | 12 | 13 | 14 | Rigor Score | 15 | 16 | 17 | 18 | Clarity & Presentation Score | 19 | 20 | 21 | Applicability Score | 22 | 23 | Editorial Independence Score |
|----------|---|---|---|------------------------|---|---|---|---|-------------------------------|---|---|---|---|---|---|---|--------------|---|---|---|--------------|---|---|------------------------|
| Rater#1  | 2 | 2 | 2 | 6                      | 1 | 1 | 1 | 1 | 4 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 8 | 3 | 3 | 3 | 7 | 1 | 1 | 1 | 3 | 1 | 1 | 2 |
| Rater#2  | 4 | 4 | 2 | 10                     | 2 | 2 | 2 | 2 | 8 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 7 | 1 | 2 | 1 | 1 | 5 | 1 | 1 | 1 | 3 | 1 | 1 | 4 |
| Rater#3  | 1 | 1 | 2 | 4                      | 1 | 1 | 2 | 1 | 5 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 7 | 1 | 2 | 1 | 1 | 5 | 1 | 1 | 1 | 3 | 1 | 1 | 1 |
| Rater#4  | 2 | 3 | 2 | 7                      | 1 | 1 | 2 | 1 | 5 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 7 | 2 | 3 | 1 | 1 | 7 | 1 | 1 | 1 | 3 | 1 | 1 | 1 |
| Rater#5  | 3 | 1 | 2 | 6                      | 1 | 1 | 3 | 1 | 6 | 1 | 1 | 2 | 2 | 1 | 1 | 1 | 9 | 1 | 1 | 1 | 1 | 4 | 1 | 1 | 1 | 3 | 1 | 1 | 2 |

Obtained Score: 33
Minimal Score: 28
Maximum Score: 60
Obtained-Minimal: 18
Maximum-Minimal: 45

Standardized Domain Scores: 40

| Question | 1 | 2 | 3 | Scope & Purpose Score | 4 | 5 | 6 | 7 | Stakeholder Involvement Score | 8 | 9 | 10 | 11 | 12 | 13 | 14 | Rigor Score | 15 | 16 | 17 | 18 | Clarity & Presentation Score | 19 | 20 | 21 | Applicability Score | 22 | 23 | Editorial Independence Score |
| Rater#2  | 4 | 4 | 4 | 12 | 2 | 1 | 2 | 1 | 6                              | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 7               | 3 | 1 | 4 | 4 | 12               | 1 | 1 | 1 | 3               | 1 | 1 | 2               |
| Rater#3  | 3 | 3 | 3 | 9  | 3 | 1 | 2 | 2 | 8                              | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 8               | 3 | 1 | 4 | 3 | 11               | 1 | 2 | 2 | 5               | 1 | 2 | 3               |
| Rater#4  | 4 | 3 | 2 | 9  | ? | 1 | 3 | 1 | 5                              | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 1 | 8               | 3 | 2 | 4 | 1 | 10               | 2 | 1 | 1 | 4               | 1 | 1 | 2               |
| Rater#5  | 4 | 4 | 4 | 12 | ? | 1 | 1 | 1 | 3                              | 1 | 1 | 1 | 4 | 2 | 1 | 1 | 1 | 11              | 3 | 4 | 4 | 11              | 1 | 1 | 1 | 3               | 1 | 1 | 2               |
| Rater#6  | 4 | 4 | 4 | 12 | 1 | 1 | 4 | 1 | 7                              | 3 | 3 | 4 | 2 | 2 | 1 | 1 | 1 | 16              | 4 | 3 | 4 | 4 | 15               | 1 | 1 | 1 | 3               | 1 | 1 | 2               |
| Rater#7  | 1 | 3 | 1 | 5  | 2 | 1 | 1 | 1 | 5                              | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 7               | 4 | 1 | 3 | 3 | 11               | 4 | 1 | 1 | 3               | 1 | 1 | 1               |

Obtained Score 59
Minimum Score 18
Maximum Score 72
Obtained-Minimal 41
Maximum-Minimal 54

Standardized Domain Scores 76


| Question | 1 | 2 | 3 | Scope & Purpose Score | 4 | 5 | 6 | 7 | Stakeholder Involvement Score | 8 | 9 | 10 | 11 | 12 | 13 | 14 | Rigor Score | 15 | 16 | 17 | 18 | Clarity & Presentation Score | 19 | 20 | 21 | Applicability Score | 22 | 23 | Editorial Independence Score |
| Rater#1  | 3 | 3 | 1 | 7  | 4 | 1 | 3 | 1 | 9                              | 2 | 3 | 1 | 4 | 3 | 13 | 4 | 4 | 4 | 2 | 10               | 1 | 1 | 1 | 3               | 4 | 4 | 4               |
| Rater#2  | 3 | 3 | 2 | 8  | 4 | 1 | 3 | 1 | 9                              | 1 | 1 | 1 | 3 | 1 | 1 | 1 | 1 | 9               | 4 | 3 | 1 | 8               | 1 | 1 | 1 | 3               | 1 | 1 | 4               |
| Rater#3  | 3 | 3 | 2 | 8  | 4 | 1 | 2 | 1 | 8                              | 2 | 3 | 2 | 3 | 3 | 2 | 3 | 18              | 3 | 4 | 3 | 2 | 12               | 2 | 2 | 2 | 6               | 2 | 2 | 5               |
| Rater#4  | 3 | 3 | 3 | 9  | 4 | 1 | 2 | 1 | 8                              | 3 | 1 | 1 | 2 | 1 | 1 | 10 | 3 | 3 | 3 | 1 | 10               | 1 | 1 | 1 | 2               | 1 | 3 | 4               |
| Rater#6  | 4 | 4 | 4 | 12 | 3 | 1 | 4 | 2 | 10                             | 2 | 2 | 3 | 2 | 3 | 2 | 1 | 15              | 4 | 4 | 4 | 4 | 16               | 3 | 2 | 1 | 6               | 2 | 2 | 3               |

Obtained Score 44
Minimum Score 15
Maximum Score 60
Obtained-Minimal 29
Maximum-Minimal 45

Standardized Domain Scores 64

POGO Emetogenicity Classification Guidelines
APPENDIX D: CATEGORIES AND GRADES OF EVIDENCE

NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1 The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3 The recommendation is based on any level of evidence but reflects major disagreement.

QUALITY OF EVIDENCE

High Quality Further research is very unlikely to change our confidence in the estimate of effect

Moderate Quality Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low Quality Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very Low Quality Any estimate of effect is very uncertain

GRADES FOR RECOMMENDATIONS

<table>
<thead>
<tr>
<th>Grade of Recommendation</th>
<th>Benefit vs Risk and Burdens</th>
<th>Methodology</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>Desirable effects clearly outweigh undesirable effects or vice versa</td>
<td>Evidence from well done RCTs or Exceptional observational studies</td>
<td>Apply to most patients in most circumstances Further research unlikely to change recommendation</td>
</tr>
<tr>
<td>1B</td>
<td>Desirable effects clearly outweigh undesirable effects or vice versa</td>
<td>Evidence from RCTs with some flaws in study or Very strong evidence from observational studies</td>
<td>Apply to most patients in most circumstances Further research might be helpful</td>
</tr>
<tr>
<td>1C</td>
<td>Desirable effects clearly outweigh undesirable effects or vice versa</td>
<td>Evidence of at least one critical outcome from observational studies, case series or RCTs with flaws</td>
<td>Apply to most patients in many circumstances Further research would be helpful</td>
</tr>
<tr>
<td>2A</td>
<td>Desirable effects closely balanced with undesirable effects</td>
<td>Consistent evidence from RCTs without important flaws or Exceptionally strong evidence from observational studies</td>
<td>Best action may depend on circumstances or patient or society values Further research unlikely to change recommendation</td>
</tr>
<tr>
<td>2B</td>
<td>Desirable effects closely balanced with undesirable effects</td>
<td>Evidence from RCTs with important flaws or Very strong evidence from observational studies</td>
<td>Best action dependent on patient circumstances or patient or society values Further research may change recommendation</td>
</tr>
<tr>
<td>2C</td>
<td>Desirable effects closely balanced with undesirable effects</td>
<td>Evidence of at least one critical outcome from observational studies, case series or RCTs with serious flaws</td>
<td>Other alternatives may be equally reasonable Further research very likely to change recommendation</td>
</tr>
</tbody>
</table>
APPENDIX E: ALPHABETICAL LIST OF ANTINEOPLASTIC AGENT AND EMETIC RISK

Note: All agents are given intravenously (IV) unless otherwise stated.

<table>
<thead>
<tr>
<th>Antineoplastic Agent</th>
<th>Level of Emetic Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Fluorouracil</td>
<td>Low</td>
</tr>
<tr>
<td>Aldesleukin &gt; 12 to 15 million units/m²</td>
<td>Moderate</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Minimal</td>
</tr>
<tr>
<td>Alpha interferon</td>
<td>Minimal</td>
</tr>
<tr>
<td>Altretamine</td>
<td>High</td>
</tr>
<tr>
<td>Amifostine &gt; 300 mg/m²</td>
<td>Moderate</td>
</tr>
<tr>
<td>Amifostine ≤ 300 mg/m²</td>
<td>Low</td>
</tr>
<tr>
<td>Amsacrine</td>
<td>Low</td>
</tr>
<tr>
<td>Anthracycline + cyclophosphamide</td>
<td>High</td>
</tr>
<tr>
<td>*Cyclophosphamide + doxorubicin</td>
<td>High</td>
</tr>
<tr>
<td>*Cyclophosphamide + epirubicin</td>
<td>High</td>
</tr>
<tr>
<td>Arsenic trioxide</td>
<td>Moderate</td>
</tr>
<tr>
<td>Asparaginase (IM or IV)</td>
<td>Minimal</td>
</tr>
<tr>
<td>Azacitidine</td>
<td>Moderate</td>
</tr>
<tr>
<td>Bendamustine</td>
<td>Moderate</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Minimal</td>
</tr>
<tr>
<td>Bexarotene</td>
<td>Low</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>Minimal</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Minimal</td>
</tr>
<tr>
<td>Busulfan</td>
<td>Moderate</td>
</tr>
<tr>
<td>Busulfan (oral)</td>
<td>Low</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>Low</td>
</tr>
<tr>
<td>Carboplatin*</td>
<td>High</td>
</tr>
<tr>
<td>Carmustine &gt; 250 mg/m²</td>
<td>High</td>
</tr>
<tr>
<td>Carmustine ≤ 250 mg/m²</td>
<td>Moderate</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Minimal</td>
</tr>
<tr>
<td>Chlorambucil (oral)</td>
<td>Minimal</td>
</tr>
<tr>
<td>Cisplatin*</td>
<td>High</td>
</tr>
<tr>
<td>Cladribine (2-chlorodeoxyadenosine)</td>
<td>Minimal</td>
</tr>
<tr>
<td>Clofarabine*</td>
<td>Moderate</td>
</tr>
<tr>
<td>Cyclophosphamide (oral)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Cyclophosphamide &lt; 1 g/m²”</td>
<td>Moderate</td>
</tr>
<tr>
<td>Cyclophosphamide ≥ 1 g/m²”</td>
<td>High</td>
</tr>
<tr>
<td>Cyclophosphamide + anthracycline</td>
<td>High</td>
</tr>
<tr>
<td>*Cyclophosphamide + doxorubicin</td>
<td>High</td>
</tr>
<tr>
<td>*Cyclophosphamide + epirubicin</td>
<td>High</td>
</tr>
<tr>
<td>Cyclophosphamide + etoposide</td>
<td>High</td>
</tr>
<tr>
<td>Cytarabine &gt; 200 mg to &lt; 3 g/m²</td>
<td>Moderate</td>
</tr>
<tr>
<td>Cytarabine ≤ 200 mg/m²</td>
<td>Low</td>
</tr>
<tr>
<td>Cytarabine 3 g/m²/dose*</td>
<td>High</td>
</tr>
<tr>
<td>Cytarabine 150-200 mg/m² + daunorubicin*</td>
<td>High</td>
</tr>
<tr>
<td>Antineoplastic Agent</td>
<td>Level of Emetic Risk</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Cytarabine 300 mg/m² + etoposide*</td>
<td>High</td>
</tr>
<tr>
<td>Cytarabine 300 mg/m² + teniposide*</td>
<td>High</td>
</tr>
<tr>
<td>Cytarabine, methotrexate + hydrocortisone: Intrathecal therapy*</td>
<td>Moderate</td>
</tr>
<tr>
<td>Daclcarbazine</td>
<td>High</td>
</tr>
<tr>
<td>Dactinomycin*</td>
<td>High</td>
</tr>
<tr>
<td>Daunorubicin*</td>
<td>Moderate</td>
</tr>
<tr>
<td>Daunorubicin + cytarabine 150-200 mg/m² *</td>
<td>High</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>Minimal</td>
</tr>
<tr>
<td>Decitabine</td>
<td>Minimal</td>
</tr>
<tr>
<td>Denileukin diftitox</td>
<td>Minimal</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Minimal</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Low</td>
</tr>
<tr>
<td>Doxorubicin (liposomal)</td>
<td>Low</td>
</tr>
<tr>
<td>Doxorubicin*</td>
<td>Moderate</td>
</tr>
<tr>
<td>Doxorubicin + cyclophosphamide*</td>
<td>High</td>
</tr>
<tr>
<td>Doxorubicin + ifosfamide*</td>
<td>High</td>
</tr>
<tr>
<td>Doxorubicin + methotrexate 5 g/m²</td>
<td>High</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>Moderate</td>
</tr>
<tr>
<td>Epirubicin + cyclophosphamide*</td>
<td>High</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Minimal</td>
</tr>
<tr>
<td>Etoposide</td>
<td>Low</td>
</tr>
<tr>
<td>Etoposide (oral)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Etoposide + cyclophosphamide*</td>
<td>High</td>
</tr>
<tr>
<td>Etoposide + cytarabine 300 mg/m² *</td>
<td>High</td>
</tr>
<tr>
<td>Etoposide + ifosfamide*</td>
<td>High</td>
</tr>
<tr>
<td>Fludarabine</td>
<td>Minimal</td>
</tr>
<tr>
<td>Fludarabine (oral)</td>
<td>Low</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>Minimal</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Low</td>
</tr>
<tr>
<td>Gemtuzumab ozogamicin</td>
<td>Minimal</td>
</tr>
<tr>
<td>Hydrocortisone, cytarabine + methotrexate: Intrathecal therapy*</td>
<td>Moderate</td>
</tr>
<tr>
<td>Hydroxyurea (oral)</td>
<td>Minimal</td>
</tr>
<tr>
<td>Idarubicin</td>
<td>Moderate</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>Moderate</td>
</tr>
<tr>
<td>Ifosfamide + doxorubicin*</td>
<td>High</td>
</tr>
<tr>
<td>Ifosfamide + etoposide*</td>
<td>High</td>
</tr>
<tr>
<td>Imatinib (oral)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Intrathecal therapy (methotrexate, hydrocortisone &amp; cytarabine)*</td>
<td>Moderate</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>Moderate</td>
</tr>
<tr>
<td>Ixabepilone</td>
<td>Low</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>Minimal</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>Minimal</td>
</tr>
<tr>
<td>Lomustine</td>
<td>Moderate</td>
</tr>
<tr>
<td>Mechlorethamine</td>
<td>High</td>
</tr>
<tr>
<td>Melphalan (oral low-dose)</td>
<td>Minimal</td>
</tr>
<tr>
<td>Antineoplastic Agent</td>
<td>Level of Emetic Risk</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Melphalan ( \geq 50 \text{ mg/m}^2 )</td>
<td>Moderate</td>
</tr>
<tr>
<td>Methotrexate ( \geq 250 \text{ mg/m}^2 ) to ( &lt; 12 \text{ g/m}^2 )</td>
<td>Moderate</td>
</tr>
<tr>
<td>Methotrexate ( \geq 12 \text{ g/m}^2 )</td>
<td>High</td>
</tr>
<tr>
<td>Methotrexate ( \geq 250 \text{ mg/m}^2 ) to ( &lt; 12 \text{ g/m}^2 )</td>
<td>Moderate</td>
</tr>
<tr>
<td>Methotrexate ( &gt; 50 \text{ mg/m}^2 )</td>
<td>Moderate</td>
</tr>
<tr>
<td>Methotrexate ( \leq 50 \text{ mg/m}^2 )</td>
<td>Minimal</td>
</tr>
<tr>
<td>Methotrexate ( \geq 5 \text{ g/m}^2 ) + Doxorubicin</td>
<td>High</td>
</tr>
<tr>
<td>Methotrexate, hydrocortisone + cytarabine: Intrathecal therapy*</td>
<td>Moderate</td>
</tr>
<tr>
<td>Mitomycin</td>
<td>Low</td>
</tr>
<tr>
<td>Methotrexate, hydrocortisone + cytarabine: Intrathecal therapy*</td>
<td>Moderate</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>Low</td>
</tr>
<tr>
<td>Nelarabine</td>
<td>Minimal</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>Low</td>
</tr>
<tr>
<td>Oxaliplatin ( &gt; 75 \text{ mg/m}^2 )</td>
<td>Moderate</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Low</td>
</tr>
<tr>
<td>Paclitaxel-albumin</td>
<td>Low</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>Minimal</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>Low</td>
</tr>
<tr>
<td>Pentostatin</td>
<td>Minimal</td>
</tr>
<tr>
<td>Procarbazine (oral)</td>
<td>High</td>
</tr>
<tr>
<td>Methotrexate ( \geq 12 \text{ g/m}^2 )</td>
<td>High</td>
</tr>
<tr>
<td>Methotrexate, hydrocortisone + cytarabine: Intrathecal therapy*</td>
<td>Moderate</td>
</tr>
<tr>
<td>Temozolomide (oral)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>Minimal</td>
</tr>
<tr>
<td>Teniposide</td>
<td>Low</td>
</tr>
<tr>
<td>Teniposide + cytarabine 300 mg/m² *</td>
<td>High</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Minimal</td>
</tr>
<tr>
<td>Thioguanine (oral)</td>
<td>Minimal</td>
</tr>
<tr>
<td>Thiotepa ( &lt; 300 \text{ mg/m}^2 )</td>
<td>Low</td>
</tr>
<tr>
<td>Thiotepa ( \geq 300 \text{ mg/m}^2 )</td>
<td>High</td>
</tr>
<tr>
<td>Topotecan</td>
<td>Low</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Minimal</td>
</tr>
<tr>
<td>Valrubicin</td>
<td>Minimal</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>Minimal</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Minimal</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>Minimal</td>
</tr>
<tr>
<td>Vinorelbine (oral)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Vorinostat</td>
<td>Low</td>
</tr>
</tbody>
</table>

*Pediatric evidence available

**Note:** All agents given intravenously (IV) unless stated otherwise

**High** = High Level of Emetic Risk (> 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 (10-30% frequency of emesis in absence of prophylaxis)

**Minimal** = Minimal Level of Emetic Risk (<10% frequency of emesis in absence of prophylaxis)
FEEDBACK QUESTIONNAIRE

POGO Antineoplastic-induced Nausea and Vomiting Guideline Development Group
Guideline for the Classification of the Acute Emetogenic Potential for Antineoplastic Medication in Pediatric Cancer Patients

The panel that developed the practice guideline will consider all of your feedback, along with that from other reviewers. The panel will use this feedback to revise the guideline report and refine the recommendations.

1. What is your role in the care of pediatric patients with cancer?
   - [ ] Oncologist
   - [ ] Hematologist
   - [ ] Social worker
   - [ ] Nurse
   - [ ] Psychologist
   - [ ] Pharmacist
   - [ ] Administrator
   - [ ] Nurse Practitioner
   - [ ] Other (please specify): ______________________________

2. Do you currently follow a practice guideline on Emetogenicity Classification?
   - [ ] No
   - [ ] Yes (please specify): ______________________________________________________________

   Is the guideline you are using consistent with this guideline:  [ ] No  [ ] Yes

3. The following items ask about the draft Guideline for the Classification of the Acute Emetogenic Potential for Antineoplastic Medication in Pediatric Cancer Patients developed by the POGO Antineoplastic-induced Nausea and Vomiting Guideline Development Group:

   For each item below, please check off the box that most adequately reflects your opinion.

<table>
<thead>
<tr>
<th>Item</th>
<th>Strongly Agree</th>
<th>Neither Agree nor Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. The rationale for developing a guideline, as stated in the “Introduction” and “Scope and Purpose” sections of the draft guideline, is clear.</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>b. There is a need for a Canadian practice guideline on Emetogenicity Classification.</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>c. The literature search described in the draft guideline is complete (no key studies or guidelines were missed).</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>d. The evidence described in the draft guideline is relevant.</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>e. I agree with the methods used to summarize the evidence included in the draft guideline.</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>f. The results of the studies described in the draft guideline are interpreted according to my understanding of the data.</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>g. The draft recommendations are clear.</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>h. I agree with the draft recommendations as stated.</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>i. I would feel comfortable having these recommendations applied in my hospital.</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>
How likely would you be to adopt of these recommendations in your own practice?

[ ] Very Likely  [ ] Unsure  [ ] Not At All Likely  [ ] Not applicable

Please feel free to add comments below. Among other issues, you may wish to comment on the clarity and completeness of the guideline, the wording of specific recommendations, the links between the available evidence and the recommendations, and any significant gaps in the recommendations.

________________________________________________________________________________________
________________________________________________________________________________________
________________________________________________________________________________________
________________________________________________________________________________________

When you have completed the questionnaire, please return it by fax or e-mail to:

Carla Bennett  
Coordinator of Clinical Programs  
480 University Ave. Suite 1014  
Toronto, ON M5G 1V2  
Fax: 416-592-1285  
e-mail: cbennett@pogo.ca
APPENDIX G: STAKEHOLDER REVIEWER SURVEY

STAKEHOLDER FEEDBACK QUESTIONNAIRE

POGO Antineoplastic-induced Nausea and Vomiting Guideline Development Group
Guideline for the Classification of the Acute Emetogenic Potential for Antineoplastic Medication in Pediatric Cancer Patients

Thank you for participating in the external review of the Emetogenicity Classification Guideline prepared by the Antineoplastic – induced Nausea and Vomiting Guideline Development Group of the Pediatric Oncology Group of Ontario (POGO).

You have been sent both a full guideline, which includes information about the development process of this guideline, as well as a quick review guideline which summarizes the key recommendations.

You have been chosen as a representative of your institution or agency and for your expertise in your field.

We would appreciate you reading both documents and then completing the survey which should only take a few minutes.

The panel that developed the practice guideline will consider all of your feedback, along with that from other reviewers. The panel will use this feedback to revise the guideline report and refine the recommendations.

1. Please indicate your agreement with the following statements with regard to the Guideline for the Classification of the Acute Emetogenic Potential for Antineoplastic Medication in Pediatric Cancer Patients:

<table>
<thead>
<tr>
<th>For each item below, please check off the box that most adequately reflects your opinion.</th>
<th>Strongly Agree</th>
<th>Neither Agree nor Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. The rationale for developing a guideline, as stated in the &quot;Introduction&quot; and &quot;Scope and Purpose&quot; sections of the draft guideline, is clear.</td>
<td>☐ ☐ ☐ ☐ ☐</td>
<td>☐ ☐ ☐ ☐ ☐</td>
<td>☐ ☐ ☐ ☐ ☐</td>
</tr>
<tr>
<td>b. There is a need for a practice guideline on Emetogenicity Classification.</td>
<td>☐ ☐ ☐ ☐ ☐</td>
<td>☐ ☐ ☐ ☐ ☐</td>
<td>☐ ☐ ☐ ☐ ☐</td>
</tr>
<tr>
<td>c. The literature search described in the guideline is relevant and complete.</td>
<td>☐ ☐ ☐ ☐ ☐</td>
<td>☐ ☐ ☐ ☐ ☐</td>
<td>☐ ☐ ☐ ☐ ☐</td>
</tr>
<tr>
<td>d. The results of the studies described in the guideline are interpreted according to my understanding of the data.</td>
<td>☐ ☐ ☐ ☐ ☐</td>
<td>☐ ☐ ☐ ☐ ☐</td>
<td>☐ ☐ ☐ ☐ ☐</td>
</tr>
<tr>
<td>e. The draft recommendations are clear.</td>
<td>☐ ☐ ☐ ☐ ☐</td>
<td>☐ ☐ ☐ ☐ ☐</td>
<td>☐ ☐ ☐ ☐ ☐</td>
</tr>
<tr>
<td>f. I agree with the draft recommendations as stated.</td>
<td>☐ ☐ ☐ ☐ ☐</td>
<td>☐ ☐ ☐ ☐ ☐</td>
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<td>g. This guideline should be approved by POGO.</td>
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<tr>
<td>h. I would feel comfortable having these recommendations applied in my hospital.</td>
<td>☐ ☐ ☐ ☐ ☐</td>
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</tbody>
</table>

2. If this guideline is approved, how likely would you be to adopt these recommendations in your own practice?

<table>
<thead>
<tr>
<th>Very Likely</th>
<th>Unsure</th>
<th>Not At All Likely</th>
<th>Not applicable</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
</tbody>
</table>
3. At what institution do you work?

- Alberta Children’s Hospital
- British Columbia’s Children’s Hospital
- CancerCare Manitoba
- Centre hospitalier universitaire de Québec
- Centre hospitalier universitaire de Sherbrooke
- Orillia Soldier’s Memorial Hospital
- Children’s Hospital of Eastern Ontario
- Children’s Hospital, London Health Sciences Centre
- Saskatoon Cancer Centre
- Credit Valley Hospital
- Grand River Hospital
- Hôpital Sainte-Justine
- The Hospital for Sick Children
- IWK Health Centre
- Janeway Child Health Centre
- Kingston General Hospital
- McMaster University
- Montreal Children’s Hospital
- Rouge Valley Health System
- Southlake Regional Health Centre
- Stollery Children’s Hospital
- Sudbury Regional Hospital
- Windsor Regional Hospital

4. What is your role in the care of pediatric patients with cancer?

- Oncologist
- Hematologist
- Social worker
- Nurse
- Psychologist
- Pharmacist
- Administrator
- Nurse Practitioner
- Other (please specify): ______________

Please feel free to add comments below. Among other issues, you may wish to comment on the clarity and completeness of the guideline, the wording of specific recommendations, the links between the available evidence and the recommendations, and any significant gaps in the recommendations.

________________________________________________________________________________________

________________________________________________________________________________________

________________________________________________________________________________________

________________________________________________________________________________________

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________________________________________________________________________________________

________________________________________________________________________________________

When you have completed the questionnaire, please return it by fax or e-mail to:
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Toronto, ON M5G 1V2
Fax: 416-592-1285
E-mail: cbennett@pogo.ca