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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
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.

Table 1: Classification of the Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Cancer Patients Given as Single Agents

High Level of Emetic Risk (> 90% frequency of emesis in absence of prophylaxis)	
Altretamine	*Dactinomycin
*Carboplatin	Mechlorethamine
Carmustine > 250 mg/m^2	*Methotrexate ≥ 12 g/m^2
*Cisplatin	Procarbazine (oral)
*Cyclophosphamide ≥ 1 g/m^2	Streptozocin
*Cytarabine 3 g/m^2/dose	*Thiotepa ≥ 300 mg/m^2
Dacarbazine	
Moderate Level of Emetic Risk (30-90% frequency of emesis in absence of prophylaxis)	
Aldesleukin > 12 to 15 million units/m^2	Etoposide (oral)
Amifostine > 300 mg/m^2	Idarubicin
Arsenic trioxide	Ifosfamide
Azacitidine	Imatinib (oral)
Bendamustine	*Intrathecal therapy (methotrexate, hydrocortisone & cytarabine)
Busulfan	Irinotecan
*Carmustine ≤ 250 mg/m^2	Lomustine
*Clofarabine	Melphalan > 50 mg/m^2
*Cyclophosphamide < 1 g/m^2	Methotrexate ≥ 250 mg to < 12 g/m^2
Cyclophosphamide (oral)	Oxaliplatin > 75 mg/m^2
Cytarabine > 200 mg/m^2 to < 3 g/m^2	Temozolomide (oral)
*Daunorubicin	Vinorelbine (oral)
*Doxorubicin	
Epirubicin	
Low Level of Emetic Risk (10-<30% frequency of emesis in absence of prophylaxis)	
Amifostine ≤ 300 mg/m^2	Ixabepilone
Amsacrine	Methotrexate > 50 mg/m^2 to < 250 mg/m^2
Bexarotene	Mitomycin
*Busulfan (oral)	Mitoxantrone
Capecitabine	Nilotinib
Cytarabine ≤ 200 mg/m^2	Paclitaxel
Docetaxel	Paclitaxel-albumin
Doxorubicin (liposomal)	Pemetrexed
Etoposide	Teniposide
Fludarabine (oral)	Thiotepa < 300 mg/m^2
5-Fluorouracil	Topotecan
Gemcitabine	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)

Minimal (<10% frequency of emesis in absence of prophylaxis)	
Alemtuzumab	Lenalidomide
Alpha interferon	Melphalan (oral low-dose)
Asparaginase (IM or IV)	Mercaptopurine (oral)
Bevacizumab	Methotrexate ≤ 50 mg/m^2
Bleomycin	Nelarabine
Bortezomib	Panitumumab
Cetuximab	Pentostatin
Chlorambucil (oral)	Rituximab
Cladribine (2-chlorodeoxyadenosine)	Sorafenib
Decitabine	Sunitinib
Denileukin diftitox	Temsirolimus
Dasatinib	Thalidomide
Dexrazoxane	Thioguanine (oral)
Erlotinib	Trastuzumab
Fludarabine	Valrubicin
Gefitinib	Vinblastine
Gemtuzumab ozogamicin	Vincristine
Hydroxyurea (oral)	Vindesine
Lapatinib	Vinorelbine

* 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

High Level of Emetic Risk (> 90% frequency of emesis in absence of prophylaxis)
Cyclophosphamide + anthracycline
*Cyclophosphamide + doxorubicin
*Cyclophosphamide + epirubicin
*Cyclophosphamide + etoposide
*Cytarabine 150-200 mg/m^2 + daunorubicin
*Cytarabine 300 mg/m^2 + etoposide
*Cytarabine 300 mg/m^2 + teniposide
*Doxorubicin + ifosfamide
Doxorubicin + methotrexate 5 g/m^2
*Etoposide + ifosfamide

* 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.[1] Available evidence indicates that several commonly administered chemotherapy regimens produce significant AINV even with administration of the best available antiemetic strategies.[2] 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, co-incident 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 inter-disciplinary 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.[3] 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[3] 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[38, 39] 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[4-7] or for use in children[8, 9] 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"[7] 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[3] 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[10] 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[5] 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, thiotepa, 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).

SUPPORTING EVIDENCE AND INFORMATION FOR RECOMMENDATIONS

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/m^2
- *Cisplatin
- *Cyclophosphamide ≥ 1 g/m^2
- *Cytarabine 3 g/m^2/dose
- Dacarbazine
- *Dactinomycin
- Mechlorethamine
- *Methotrexate ≥ 12 g/m^2
- Procarbazine (oral)
- Streptozocin
- *Thiotepa ≥ 300 mg/m^2

* 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[10] 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 1: Summary of Pediatric Evidence Used to Inform Recommendation 1

Studies	Results
Studies where no antiemetic prophylaxis was given in at least one arm:	
Hayes FA et al. 1981[11]	• observational study • 22 patients aged 0.8 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 • no antiemetic prophylaxis mentioned • 1 child did not vomit during cisplatin infusion
Komada Y et al. 1999[12]	• observational study • 25 children aged 1 to 14 yrs given **cytarabine** 3 g/m^2 with no antiemetic prophylaxis • no vomiting observed in 8% of children
Saarinen UM et al. 1991[13]	• observational study • 9 children undergoing conditioning for bone marrow transplant with **thiotepa** 375 mg/m^2/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/m^2 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)

Studies	Results
Studies where antiemetic prophylaxis was given:	
Berrak SG et al. 2007[15]	• randomized, double blind, cross over study • 18 patients (1 to 23 yrs) randomly received 1 of 2 granisetron doses on alternating courses of **carboplatin** 175 mg/m^2 - containing therapy • 225 treatment courses evaluated, some of which may have included vincristine • 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
Hewitt M et al. 1991[16]	• observational study • 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 • ondansetron given for AINV prophylaxis • children experienced no vomits or retches on 60% of days where **cyclophosphamide** was given
Holdsworth MT et al. 2006[2] (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 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)
Kusnierczyk NMA et al. 2002[17] (supplementary data)	• observational study • 25 children undergoing conditioning for bone marrow transplant with various regimens given ondansetron + dexamethasone for AINV prophylaxis • no vomiting observed in 8/9 (89%) of children on first day of administration of **cyclophosphamide** 50 mg/kg/day
Lafay-Cousin L et al. 2000[18]	• observational study • 18 children undergoing conditioning for bone marrow transplant with **thiotepa** 300 mg/m^2/day for 3 consecutive days given ondansetron for AINV prophylaxis • no vomiting observed in 4 children (22%) • timeframe of vomiting relative to **thiotepa** administration unknown
Miyajima Y et al. 1994[19]	• non-randomized cross-over study • 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 • 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 • no vomiting observed in 0% of courses where metoclopramide + promethazine given as AINV prophylaxis
Nahata MC et al 1996[20]	• non-randomized study • 17 children undergoing conditioning for bone marrow transplant given ondansetron and other antiemetics • 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) • 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

Table 1: Summary of Pediatric Evidence Used to Inform Recommendation 1 (continued)

Studies	Results
Studies where antiemetic prophylaxis was given (continued):	
Pinkerton CR et al 1990[21]	• 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 **cisplatin**-containing (60 – 100 mg/m^2) cycles (N=6) • no vomiting observed on day 1 in 92% of **carboplatin**-containing cycles (N=12; 6 of which included carboplatin alone)
Uysal KM et al. 1999[22]	• observational study • 22 children aged 3 to 18 yrs given tropisetron for AINV prophylaxis over 125 antineoplastic cycles • no vomiting and no nausea observed on day 1 of the course in 0/7 of **cisplatin**-containing courses given without corticosteroid and in 5/10 of cisplatin-containing courses given with corticosteroid • cisplatin given in doses of 120 mg/m^2 or 20 mg/m^2

Discussion

Available pediatric experience confirms the source guideline's ranking of cisplatin ≥ 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[10] are:

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

Carboplatin

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.[21] 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.[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.[15] 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/m^2 or more. This finding was confirmed by pediatric experience.[2, 11, 19, 21, 22] In addition, investigators described poor AINV control associated with cisplatin doses less than 50 mg/m^2. Sumer et al conducted a randomized cross-over study to compare AINV associated with cisplatin 45 mg/m^2 given over 2 hours with or without dexamethasone prophylaxis.[14] 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/m^2 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/m^2.[22] 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/m^2 with tropisetron prophylaxis was associated with an AINV incidence of 100%. This level of response to tropisetron prophylaxis would place cisplatin 20 mg/m^2 as a high-risk emetogen.

Cyclophosphamide

Several pediatric studies have confirmed the high emetogenicity of cyclophosphamide in doses of 1.5 g/m^2 (50 mg/kg) or more.[2, 16, 17] 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/m^2 (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/m^2 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/m^2 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).[19] 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/m^2 and conventional AINV prophylaxis vomited during the monitoring period. This level of response to metoclopramide plus promethazine prophylaxis would place cytarabine 3 g/m^2 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/m^2 on day 1, daunorubicin and L-asparaginase on day 3 and oral dexamethasone from day 1 through 7.[12] 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/m^2 as a high-risk emetogen.

In the above-mentioned observational study by Holdsworth et al[2], 4 of 9 children (44%) who received cytarabine 3 g/m^2 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/m^2 as a high-risk emetogen.

Dactinomycin

A single study was identified that described dactinomycin-associated AINV.[2] 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 µcg/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/m^2

The AINV experience of 7 children receiving 26 courses of methotrexate 12 g/m^2 was observed by Holdsworth et al in the aforementioned study.[2] 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/m^2 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/m^2/day for 3 consecutive days prior to HSCT and in 2 children given 200 mg/m^2/day.[20] 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/m^2/day again for HSCT conditioning and ondansetron.[18] 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/m^2/day for 3 consecutive days given without antiemetic prophylaxis to children prior to autologous transplant.[13] 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/m^2 or more.

Research Gaps

No pediatric literature was located regarding the risk of AINV in children receiving altretamine, carmustine > 250 mg/m^2, 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/m^2, cyclophosphamide 1 to 1.5 g/m^2, dactinomycin and methotrexate ≥ 12 g/m^2 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/m^2
- Amifostine > 300 mg/m^2
- Arsenic trioxide
- Azacitidine
- Bendamustine
- Busulfan > 4 mg/day
- *Carmustine ≤ 250 mg/m^2
- *Clofarabine
- *Cyclophosphamide < 1 g/m^2
- Cyclophosphamide (oral)
- Cytarabine > 200 mg/m^2 to < 3 g/m^2
- *Daunorubicin
- *Doxorubicin
- Epirubicin
- Etoposide (oral)
- Idarubicin
- Ifosfamide
- Imatinib (oral)
- *Intrathecal therapy (methotrexate, hydrocortisone and cytarabine)
- Irinotecan
- Lomustine
- Melphalan > 50 mg/m^2
- Methotrexate 250 mg/m^2 to < 12 g/m^2
- Oxaliplatin > 75 mg/m^2
- 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[10] 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

Studies	Results
Studies where no antiemetic prophylaxis was given in at least one arm:	
Holdsworth MT et al. 1998[23]	• observational study • nausea and vomiting were assessed in 37 children (1 to 17 yrs) after receipt of 87 **triple intrathecal** antineoplastic (methotrexate, hydrocortisone, cytarabine) injections with no antiemetic prophylaxis • no vomiting observed in 8/37 (22%) of patients within the first 24 hours • no nausea or vomiting observed in 5/37 (13%) of patients within the first 24 hours
Jeha S et al. 2004[24]	• phase I study of **clofarabine** 11.25 to 70 mg/m^2/day for 5 days • 25 patients evaluated aged 1 to 19 years • no information regarding AINV prophylaxis provided, if any • no nausea or vomiting observed in 6 patients (24%) overall and in 4 of 13 (31%) patients receiving clofarabine 52 mg/m^2/day
Jeha S et al. 2006[25]	• phase II study of **clofarabine** 52 mg/m^2/day for 5 days • 61 patients aged 1 to 20 years each received 1 to 11 cycles • no information regarding AINV prophylaxis provided; some patients received corticosteroid on days 1 to 3 of some cycles • grade 3 or higher nausea observed in 10 of 122 cycles
Parker RI et al. 2001[26]	• randomized, double-blind, cross-over placebo controlled trial • 26 children (2 to 17 yrs) given 146 **triple intrathecal** antineoplastic doses (22 patients: methotrexate + hydrocortisone + cytarabine; 4 patients: methotrexate) • efficacy of 2 doses of ondansetron compared against placebo • no vomiting observed in 32/51 (63%) of intrathecal treatments when placebo given

Table 2: Summary of Evidence Used to Inform Recommendation 2 (continued)

Studies	Results
Studies where antiemetic prophylaxis was given:	
Dupuis LL et al. 1999[27]	• observational study • acute vomiting and nausea assessed in 94 children (1 to 17.7 yrs) with acute lymphoblastic leukemia • no vomiting observed in most children who received **doxorubicin** given ondansetron as AINV prophylaxis
Holdsworth MT et al. 1995[28]	• observational study • nausea and vomiting assessed in 16 children (2 to 15 yrs) with acute lymphoblastic leukemia over 319 courses • each course given with or without ondansetron at clinicians' discretion • 149 courses given with no antiemetic prophylaxis • no vomiting seen in 8/27 (30%) of carmustine 60 mg/m^2 courses and in 14/34 (41%) of **cyclophosphamide** 600 mg/m^2 courses when no antiemetic prophylaxis given
Holdsworth MT et al. 2006[2] (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 response observed in 76% of 29 children receiving first course of **doxorubicin** 25 mg/m^2 or **daunomycin** 30 mg/m^2 receiving ondansetron

Discussion

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

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

Busulfan IV

The source guideline did not explicitly include information regarding IV busulfan.[9] 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.[29] Thus the dose ceiling of 4 mg/day stipulated in the source guideline is not relevant to pediatric practice and was removed. The Busulfex® product monograph describes a 43% incidence of vomiting during IV busulfan administration.[30] 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 trial[25], 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/m^2 and < 1 g/m^2. In keeping with the guideline development panel's desire to eliminate such gaps and with its conservative philosophy, cytarabine < 200 mg/m^2 to < 1 g/m^2 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 al[26] 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/m^2, idarubicin, ifosfamide, imatinib (oral), irinotecan, lomustine, melphalan > 50 mg/m^2, methotrexate 250 to < 12 g/m^2, oxaliplatin > 75 mg/m^2, 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 ≤ 300 mg/m^2
- Amsacrine
- Bexarotene
- *Busulfan (oral)
- Capecitabine
- Cytarabine ≤ 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
- Thiotepa < 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 3: Summary of Evidence Used to Inform Recommendation 3

Studies	Results
Studies where no antiemetic prophylaxis was given in at least one arm:	
Hayes FA et al. 1981[11]	• observational study • 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 • no antiemetic prophylaxis mentioned • no vomiting observed with teniposide
Studies where antiemetic prophylaxis was given:	
Kusnierczyk NMA et al. 2002[17] (supplementary data)	• observational study • 25 children undergoing conditioning for HSCT with various regimens given ondansetron for AINV prophylaxis on days when oral **busulfan** given • 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

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).[9] 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 thiotepa < 300 mg/m^2 based on the COG Supportive Care Guidelines[9];
- 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.[4-6, 9] Amsacrine was not listed in any of these documents. Cancer Care Ontario[32] and the British Columbia Cancer Agency[33] 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.[9] 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.[17] 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.[11] 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[32] and the Children's Oncology Group Supportive Care Guidelines[9] 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, thiotepa in lower doses of was classified as a low-risk emetogen based on its classification in the COG Supportive Care Guidelines.[9]

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/m^2, methotrexate 50 mg/m^2 to < 250 mg/m^2, mitoxantrone, paclitaxel, etoposide, teniposide, thiotepa and topotecan. The potential dose-dependent emetogenicity of IV etoposide merits investigation. The emetogenicity of oral busulfan also requires more rigorous evaluation.

4. SINGLE ANTINEOPLASTIC 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 diftitox
- Dasatinib
- Dexrazoxane
- Erlotinib
- Fludarabine
- Gefitinib
- Gemtuzumab ozogamicin
- Hydroxyurea (oral)
- Lapatinib
- Lenalidomide
- Melphalan (oral low-dose)
- Mercaptopurine (oral)
- Methotrexate ≤ 50 mg/m^2
- Nelarabine
- Panitumumab
- Pentostatin
- Rituximab
- Sorafenib
- Sunitinib
- Temsirolimus
- Thalidomide
- Thioguanine (oral)
- Trastuzumab
- Valrubicin
- Vinblastine
- Vincristine
- Vindesine
- Vinorelbine

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[10] 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[9] 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[9]).

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/m^2, Peg-asparaginase, ritiximab, 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:

Level of Emetic Risk	Regimen
High	• *cyclophosphamide + etoposide • *cytarabine 150-200 mg/m^2 + daunorubicin • *cytarabine 300 mg/m^2 + etoposide • *cytarabine 300 mg/m^2 + teniposide • *doxorubicin + ifosfamide • doxorubicin + methotrexate 5 g/m^2 • *etoposide + ifosfamide

* 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[10] 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

Studies	Results
Studies where no antiemetic prophylaxis was given in at least one arm:	
Holdsworth MR et al. 1995[28]	• observational study • nausea and vomiting assessed in 16 children (2 to 15 yrs) with acute lymphoblastic leukemia over 319 courses • each course given with or without ondansetron at clinicians' discretion • 149 courses given with no antiemetic prophylaxis • 9 patients received 100 courses of etoposide 150mg/m^2 + **cytarabine 300 mg/m^2** • no vomiting observed in 0/36 (0%) of **etoposide 150 mg/m^2 + cytarabine 300 mg/m^2** courses without ondansetron and in 51/64 (80%) with ondansetron
Komada Y et al. 1999[12]	• randomized study evaluating 2 doses of granisetron • first of 3 identical antineoplastic courses given without AINV prophylaxis • children (1 to 14 yrs) given **methotrexate 3 g/m^2 + vincristine 1.5 mg/m^2** • no vomiting observed in 26/74 (35%) of children receiving no prophylaxis

Table 3: Summary of Evidence Used to Inform Recommendation 5 (continued)

Studies	Results
Studies where antiemetic prophylaxis was given:	
Dick et al. 1995[34]	• 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/m^2 x 1 + daunorubicin 45 mg/m^2 daily x 2 + etoposide 100 mg/m^2 daily x 5 + cytarabine 100 mg/m^2 q12h x 10 + prednisolone 40 mg/m^2 daily x 7 + thioguanine 80 mg/m^2 daily x 5** • on day 1 of antineoplastic therapy, no vomiting was observed in 3/15 (30%) of patients receiving metoclopramide + dexamethasone and 11/15 (73%) receiving ondansetron
Holdsworth et al. 2006[2] (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 + dexamethasone as AINV prophylaxis and receiving: **carboplatin 560 mg/m^2 + etoposide 100 mg/m^2 + vincristine** (5 patients; 11 courses); **cyclophosphamide 0.8-1.2 g/m^2 + doxorubicin 25-75 mg/m^2 ± etoposide 75-125 mg/m^2 + bleomycin** (21 patients; 53 courses); **cyclophosphamide > 1 g/m^2 ± etoposide 120 mg/m^2** (9 patients; 14 courses); **cyclophosphamide 2.1 g/m^2 + vincristine + doxorubicin 25 mg/m^2 or dactinomycin 1.25-1.5 mg/m^2** (13 patients; 60 courses); **ifosfamide 1.8-3.4 mg/m^2+ etoposide 100 mg/m^2 +/- carboplatin 560 mg/m^2** (21 patients; 69 courses) • complete emetic control observed in < 80% of children given ondansetron as AINV prophylaxis and receiving: **cytarabine 150-200 mg/m^2 + daunorubicin 20-30 mg/m^2 ± etoposide, IT cytarabine + dexamethasone PO** (14 patients; 34 courses); **methotrexate 5 g/m^2 + doxorubicin 30 mg/m^2, vincristine, asparaginase, mercaptopurine oral + prednisone** (7 patients; 17 courses)
Luisi FAV et al. 2006[35]	• 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/m^2 + ifosfamide 2.5 g/m^2) or epirubicin 75 mg/m^2 + carboplatin 600 mg/m^2 or ifosfamide 2.5 g/m^2 + carboplatin 600 mg/m^2 • number of cycles of each antineoplastic regimen evaluated unknown • no vomiting, retching or nausea observed in 0% of **epirubicin 75 mg/m^2+ carboplatin 600 mg/m^2** cycles given metoclopramide and 7/11 (64%) of cycles given granisetron
Miyajima Y et al. 1994[19]	• 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/m^2 + ifosfamide 3 g/m^2** given metoclopramide + promethazine prophylaxis
Pinkerton CR et al. 1990[21]	• 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/m^2 + doxorubicin 40-60 mg/m^2** cycles (5 patients) and ~60% of courses of **cyclophosphamide 400-1000 mg/m^2 + doxorubicin 40-60 mg/m^2** (8 patients)

Table 3: Summary of Evidence Used to Inform Recommendation 5 (continued)

Studies	Results
Studies where antiemetic prophylaxis was given:	
Relling MV et al. 1993[38]	• preliminary observational study: no vomiting observed in 1 of 58 antineoplastic courses (2%) in children receiving **teniposide 200 mg/m^2 + cytarabine 300 mg/m^2** in first 8 hours despite administration of various antiemetics (e.g. phenothiazines, antihistamines) • randomized comparison study of efficacy of chlorpromazine vs chlorpromazine + lorazepam in 25 children 1.7 – 7.5 yrs) receiving teniposide 200 mg/m^2 + cytarabine 300 mg/m^2 • 3 or fewer vomits observed in the first 8 hours after initiation of antineoplastic therapy observed in 42/73 (58%) of courses
Sullivan MJ et al.1992[37]	• observational study • 15 children (3 to 11 yrs) receiving numerous cycles of various antineoplastic combination regimens with ondansetron prophylaxis • 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/m^2 + cytarabine 150 mg/m^2**; 7/8 (88%) cycles of **cyclophosphamide 600 mg/m^2 + vincristine 1.5 mg/m^2**; 1/2 (50%) cycles of **cyclophosphamide 1 g/m^2 + doxorubicin 60 mg/m^2**; 4/4 (100%) cycles of **cyclophosphamide 600 mg/m^2 + dactinomycin 1.5 mg/m^2**; 4/5 (80%) cycles of **cyclophosphamide 300 mg/m^2 + cisplatin 100 mg/m^2**; 3/3 (100%) cycles of **procarbazine 100 mg/m^2 + chlorambucil 6 mg/m^2**

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[10] 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

Expert Reviewer Comment	Panel Action / Decision
Organize results according to health questions.	Done
Divide evidence tables into no Prophylaxis/ prophylaxis.	Done
Methods: Insert brief summary of literature review in text.	Done
Results: guidelines reviewed 5 or 7?	Clarified. 6 guidelines were evaluated using AGREE. Only guidelines/citations that were not evaluated are now cited in the appendix.
Delete Hesketh from table or from entire guideline?	Hesketh classification was deleted from the table appearing with recommendation 5. Its inclusion in the text was retained.
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.	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.
Statement on page 12 "at odds".	This statement was deleted.

Table 4: Specific Feedback from Content Expert Reviewers and Results of the Guideline Development Panel's Discussion (continued)

Expert Reviewer Comment	Panel Action / Decision
No compelling argument has been made to include carboplatin, thiotepa, dactinomycin or MTX > 12 gm/m2 as highly emetogenic agents or to lower the cyclophosphamide dose threshold.	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.
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.	Done
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.	The overly broad range of the moderately emetogenic category was included as a research gap in question 1 section 2.
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.	Data regarding AINV experienced after first course of each agents listed was obtained from supplementary data provided by the authors. No change was made.
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.	NCCN guidelines state that delayed AINV may last up to 7 days after antineoplastic chemotherapy. No change was made.
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.	This information is available in the appendices.
On page 17 difficult to follow why carboplatin is based in the high emetogenic risk and most evidence is moderate emetogenic.	The conclusion of the Berrak study was changed to read "high-risk" rather than moderate-risk" emetogen.
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.	Acknowledged
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.	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.
Should include ages 18-21?	Since this age group is well-served by the adult guidelines, no change has been made.
Under tools for application (page 37) suggests pre-printed and electronic order sets. Are there plans to develop standard ones as reference or examples?	No plans are being made to create these tools or templates.

Table 4: Specific Feedback from Content Expert Reviewers and Results of the Guideline Development Panel's Discussion (continued)

Expert Reviewer Comment	Panel Action / Decision
Is it possible to have a "quick reference" and an appendix that has the major classification areas all on one page for ease of use?	A quick reference has been prepared.
The background for the classification could be referred by page # as well.	Table of contents will provide this information.
You note on page 12 that published guidelines were not accepted if the guidelines were "at odds with the clinical experience of group members." 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.	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.
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.	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.
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 "other" will likely reach this level).	The bleomycin combination has been replaced by cyclophosphamide + doxorubicin.
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.	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.

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 5: Institutions of Stakeholders Who Provided Responses

Canada	Ontario
Alberta Children's Hospital, Calgary, Alberta	Children's Hospital of Eastern Ontario, Ottawa
Janeway Child Health Centre, St. John's, Newfoundland	Children's Hospital, London Health Sciences Centre, London
Stollery Children's Hospital, Edmonton, Alberta	Credit Valley Hospital, Mississauga
	Grand River Hospital, Kitchener
	Kingston General Hospital, Kingston
	McMaster University, Hamilton
	Orillia Soldier's Memorial Hospital, Orillia
	Rouge Valley Health System, Scarborough
	Southlake Regional Health Centre, Newmarket
	Hôpital régional de Sudbury Regional Hospital, Sudbury
	The Hospital for Sick Children, Toronto
	Windsor Regional Hospital, Windsor

Table 6: Extent of Agreement of Stakeholders with Survey Statements

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:					
	Strongly Agree	**Neither Agree nor Disagree**	**Strongly Disagree**	**Rating Average**	**Response Count**
The rationale for developing a guideline, as stated in the "Introduction" and "Scope and Purpose" sections of the draft guideline, is clear.	**100.0% (29)**	0.0% (0)	0.0% (0)	3.00	29
There is a need for a practice guideline on Emetogenicity Classification.	**89.7% (26)**	10.3% (3)	0.0% (0)	2.90	29
The literature search described in the guideline is relevant and complete.	**96.6% (28)**	3.4% (1)	0.0% (0)	2.97	29
The results of the studies described in the guideline are interpreted according to my understanding of the data.	**96.6% (28)**	3.4% (1)	0.0% (0)	2.97	29
The draft recommendations are clear.	**100.0% (29)**	0.0% (0)	0.0% (0)	3.00	29
I agree with the draft recommendations as stated.	**100.0% (29)**	0.0% (0)	0.0% (0)	3.00	29
This guideline should be approved by POGO	**89.7% (26)**	10.3% (3)	0.0% (0)	2.90	29
I would feel comfortable having these recommendations applied in my hospital.	**100.0% (29)**	0.0% (0)	0.0% (0)	3.00	29
			answered question		**29**
			skipped question		**0**

Table 7: Stakeholders' opinion of likelihood of adoption of guideline in their practice.

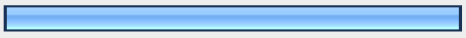
If this guideline is approved, how likely would you be to adopt these recommendations in your own practice?		Response Percent	Response Count
Very Likely		79.3%	23
Unsure		6.9%	2
Not at all likely		0.0%	0
Not applicable		13.8%	4
	answered question		29
	skipped question		0

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

Stakeholder Comment	Panel Action / Decision
In the Quick Summary AINV is not defined. In Table 1 under moderate level of emetic risk there should be a ">" 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).	AINV defined on first use in text of Quick Summary ">" " 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.
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.	Response not required.
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.	Response not required.
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.	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.
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.	These aspects of AINV are not within the scope of this guideline and will be addressed in planned future guidelines. Response not required.

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

Stakeholder Comment	Panel Action / Decision
These recommendations provided evidence-based information on the emetogenicity of antineoplastic agents. These recommendations are valuable as we introduce newer agents whose emetogenetic potential was unknown. They can be adapted and utilized for teaching purposes of new staff. Recommendations are already in place for standard meds.	Response not required.
Not a great amount of robust pediatric research to support the guidelines. Pre-printed orders would be advantageous and perhaps increase utilization of guidelines.	Response not required.
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.	Response not required.
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.	Response not required.
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.	Response not required.
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.	Response not required.
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?	Response not required.
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.	Response not required.
Great work	Response not required.

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.

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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:

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- Carol Portwine, pediatric hematologist/oncologist
- Mark Holdsworth, pediatric oncology pharmacist

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FUNDING SOURCES

Pediatric Oncology Group of Ontario
Ministry of Health and Long Term Care, Ontario
L. Sung and L.L. Dupuis received partial salary support from the Children's Oncology Group.

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APPENDIX A: LITERATURE SEARCH CRITERIA AND LIST OF CITATIONS EVALUATED AND EXCLUDED

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 nausea/ 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:

---

1 "nausea and vomiting"/ or chemotherapy induced emesis/ or nausea/ or opioid induced emesis/ or radiation induced emesis/ or retching/ or vomiting/ (107965)
2 exp Neoplasm/ (1429474)
3 1 and 2 (33653)
4 exp Antiemetic Agent/ (90027)
5 exp Antineoplastic Agent/ (695137)
6 4 and 5 (16370)
7 3 or 6 (45962)
8 limit 7 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>) (3168)
9 exp practice guideline/ (137069)
10 8 and 9 (140)
11 2 and 4 and 9 (426)
12 limit 11 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>) (34)
13 3 and 4 and 9 (245)
14 limit 13 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>) (21)
15 10 or 12 or 14 (141)
16 from 15 keep 1-141 (141)

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

---

1 (cancer: or neoplas: or oncolog:).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw] (49445)
2 (nausea or nauseous or vomit: or emesis or "anti-emetic:" or "anti emetic:" or antiemetic:).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw] (16104)
3 1 and 2 (3246)
4 (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] (111019)
5 3 and 4 (436)
6 from 5 keep 1-436 (436)

Citations Reviewed and Excluded

The Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC). Prevention of chemotherapy- and radiotherapy-induced emesis: results of the 2004 Perugia International Antiemetic Consensus Conference. Annals of Oncology. 2006;17:20-28.
Adult data; superseded by current MASCC guideline.

American Society of Health-System Pharmacists (ASHP). ASHP Therapeutic Guidelines on the Pharmacologic Management of Nausea and Vomiting in Adult and Pediatric Patients Receiving Chemotherapy or Radiation Therapy or undergoing Surgery. Am J Health Syst Pharm 1999;56(8):729-64.
Not current; method of evidence assessment unclear.

Antonarakis ES, Evans JL, Heard GF, Noonan LM, Pizer BL, Hain RD. Prophylaxis of acute chemotherapy-induced nausea and vomiting in children with cancer: what is the evidence? Pediatr Blood Cancer 2004;43(6):651-8.
Not a guideline

Antonarakis ES, Hain RD. Nausea and vomiting associated with cancer chemotherapy: drug management in theory and in practice. Arch Dis Child 2004;89(9):877-80.
Not a guideline

Billett AL, Sallan SE. Antiemetics in children receiving cancer chemotherapy. Support Care Cancer 1994;2(5):279-85.
Not a guideline

Dupuis LL, Lau R, Greenberg ML. Effectiveness of strategies for preventing acute antineoplastic-induced nausea and vomiting in children with acute lymphoblastic leukemia. Canadian Journal of Hospital Pharmacy. 1999;52(6):350-361.
Not a guideline

Dupuis LL and Nathan PC. Options for the prevention and management of acute chemotherapy-induced nausea and vomiting in children. Paediatr Drugs 2003;5(9):597-613.
Not a guideline

Durand JP, Madelaine I, Scotté F. [Guidelines for prophylaxis and treatment of chemotherapy-induced nausea and vomiting]. Bull Cancer. 2009 Oct; 96(10):951-60.
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

Herrstedt J, Roila F; ESMO Guidelines Working Group. Chemotherapy-induced nausea and vomiting: ESMO clinical recommendations for prophylaxis. Ann Oncol 2008;19 Suppl 2:ii110-2.
Adult data; incorporated into current MASCC guideline

Hesketh PJ. Chemotherapy-induced nausea and vomiting. N Engl J Med 2008;358(23):2482-94.
Not a guideline; adult data

Hesketh PJ, Kris MG, Grunberg SM, Beck T, Hainsworth JD, Harker G, Aapro MS, Gandara D, Lindley CM. Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol. 1997; 15(1):103-109.
Not a guideline

Holdsworth MT, Raisch DW, Frost J. Acute and delayed nausea and emesis control in pediatric oncology patients. Cancer 2006;106(4):931-40.
Not a guideline

Kris MG, Hesketh PJ, Somerfield MR, Feyer P, Clark-Snow R, Koeller JM, Morrow GR, Chinnery LW, Chesney MJ, Gralla RJ, Grunberg SM. American Society of Clinical Oncology (ASCO) Guideline for antiemetics in oncology: update 2006. Journal of Clinical Oncology. 2006;24:2932-2947.
Not extensively referenced

Naeim A, Dy SM, Lorenz KA, Sanati H, Walling A, Asch SM. Evidence-based recommendations for cancer nausea and vomiting. J Clin Oncol 2008;26(23):3903-10.
Not a guideline

Roila F, Hesketh PJ, Herrstedt J; Antiemetic Subcommitte of the Multinational Association of Supportive Care in Cancer. Prevention of chemotherapy- and radiotherapy-induced emesis: results of the 2004 Perugia International Antiemetic Consensus Conference. Ann Oncol 2006;17(1):20-8.
Adult data; superseded by current MASCC guideline

Pikó B, Bassam A. [Treatment of tumor therapy-induced nausea and vomiting] [Hungarian]. Magy Onkol. 2009;53(1):39-45.
Article not in English/French; [Hungarian]

Sperry ML. A review of the 2006 ASCO antiemetics guidelines update. U.S. Pharmacist. 2008;32(1):22-28.
Not a guideline

Terrie YC. Management and prevention of chemotherapy-induced nausea and vomiting. Pharmacy Times. 2009;75(8):28-30.
Not a guideline

3. LITERATURE SEARCH – EMETOGENIC 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, 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**

   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.

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

Antonarakis ES, Hain RDW. Nausea and vomiting associated with cancer chemotherapy: drug management in theory and in practice. Archives of Disease in Childhood. 2004;89:877-880.
Review; extrapolated from adult data

Billett AL, Sallan SE. Antiemetics in children receiving cancer chemotherapy. Support Care Cancer. 1994;2:279-285.
Review; expert opinion

Dolgin MJ, Katz ER. Conditioned aversions in pediatric cancer patients receiving chemotherapy. J Dev Behav Pediatr. 1988;9:82-85
Not applicable

Dolgin MJ, Katz ER, McGinty K, Siegel SE. Anticipatory nausea and vomiting in pediatric cancer patients. Pediatrics. 1985;75:547-552.
Not applicable

Dupuis L, Chan HSL, Lacey C and McBride J. The management of chemotherapy-induced nausea and vomiting in children. Can J of Hosp Pharm. 1986;39(2):38-39, 44
Review

Dupuis LL, Nathan PC. Options for the prevention and management of acute chemotherapy-induced nausea and vomiting in children. Pediatr Drugs. 2003;5(9):597-613
Review

Foot ABM, Hayes C. Audit of guidelines for effective control of chemotherapy and radiotherapy induced emesis. Arch Dis Child. 1994;71:475-480.
Not extensively referenced; institution specific protocol

Grunberg SM, Osoba D, Hesketh PJ, Gralla RJ, Borjeson SE et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity - an update. Support Care Cancer. 2005;13(2):80-84.
Review article; adult data

Hesketh PJ. Defining the emetogenicity of cancer chemotherapy regimens: relevance to clinical practice. The Oncologist. 1999;4:191-196
Adult data

Licitra L, Spinazze S, Roila F. Antiemetic therapy. Critical Reviews in Oncology/Hematology. 2002;43(1):93-101
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

Osoba D, Zee B, Pater J et al. Determinants of post-chemotherapy nausea and vomting in patients with cancer. Quality of Life and Symptom Control Committees of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 1997;15:116-123.
Adult data

Roila F, Feyer P, Maranzano E, Olver I, Clark-Snow R, Warr D, Molassiotis A. Antiemetics in children receiving chemotherapy.Support Care Cancer. 2005;13(2):129-31.
Review; expert opinion

Roila F, Aapro M, Stewart A. Optimal selection of antiemetics in children receiving cancer chemotherapy. Support Care Caner. 1998;6:215-220
Not applicable

Tyc VL, Mulhern RK, Jayawardene D, Fairclough D. Chemotherapy-induced nausea and emesis in pediatric cancer patients: an analysis of coping strategies. *J Pain Symptom Manage* 10:338-347, 1995.
Not applicable

Vanhoff J, Hockenberry-Eaton MJ, Patterson K, Hutter JJ. A survey of antiemetic use in children with cancer. American Journal of Diseases in Children. 1991;145(7):773-778.
Expert opinion

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

Ovid MEDLINE(R) 1950 to Present with Daily Update

exp Amsacrine/	1099
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)")	164
exp vomiting/ or exp antiemetics/	130661
3 and 2	8

Sung WJ, Kim DH, Sohn SK, Kim JG, Baek JH, Jeon SB, Moon JH, Ahn BM, Lee KB. Phase II trial of amsacrine plus intermediate-dose Ara-C (IDAC) with or without etoposide as salvage therapy for refractory or relapsed acute leukemia. Japanese Journal of Clinical Oncology. 2005;35(10):612-6.
Adult data

Horstmann MA, Hassenpflug WA, zur Stadt U, Escherich G, Janka G, Kabisch H. Amsacrine combined with etoposide and high-dose methylprednisolone as salvage therapy in acute lymphoblastic leukemia in children. Haematologica. 2005;90(12):1701-3.
Not applicable

Frost BM, Nygren P, Gustafsson G, Forestier E, Jonsson OG, Kanerva J, Nygaard R. Schmiegelow K. Larsson R. Lonnerholm G. Nordic Society for Paediatric Haematology and Oncology. Increased in vitro cellular drug resistance is related to poor outcome in high-risk childhood acute lymphoblastic leukaemia. British Journal of Haematology. 2003;122(3):376-85.
Not applicable

Cortes J, O'Brien SM, Pierce S, Keating MJ, Freireich EJ, Kantarjian HM. The value of high-dose systemic chemotherapy and intrathecal therapy for central nervous system prophylaxis in different risk groups of adult acute lymphoblastic leukemia. Blood. 1995;86(6):2091-7.
Adult data; not applicable

Bernasconi C, Lazzarino M, Morra E, Alessandrino EP, Pagnucco G, Resegotti L, Locatelli F, Ficarra F, Bacigalupo A, Carella AM, van Lint MT. Early intensification followed by allo-BMT or auto-BMT or a second intensification in adult ALL: a randomized multicenter study. Leukemia. 1992;6 Suppl 2:204-8.
Adult data

Willemze R, Peters WG, van Hennik MB, Fibbe WE, Kootte AM, van Berkel M, Lie R, Rodenburg CJ, Veltkamp JJ. Intermediate and high-dose ARA-C and m-AMSA (or daunorubicin) as remission and consolidation treatment for patients with relapsed acute leukaemia and lymphoblastic non-Hodgkin lymphoma. Scandinavian Journal of Haematology. 1985;34(1):83-7.
Adult data

Hines JD, Oken MM, Mazza JJ, Keller AM, Streeter RR, Glick JH. High-dose cytosine arabinoside and m-AMSA is effective therapy in relapsed acute nonlymphocytic leukemia. Journal of Clinical Oncology. 1984;2(6):545-9.
Adult data

Yap BS, Plager C, Benjamin RS, Murphy WK, Legha SS, Bodey GP. Phase II evaluation of AMSA in adult sarcomas. Cancer Treatment Reports. 1981;65(3-4):341-3.
Adult data

EMBASE 1980 to 2009 Week 30

exp amsacrine/ or exp amsacrine derivative/	3147
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>)	374
exp "nausea and vomiting"/ or exp vomiting/	121998
exp antiemetic agent/	94315
3 and 2	32
4 and 2	12
6 or 5	34

Gandemer V, Le Deley MC, Dollfus C, Auvrignon A, Bonnaure-Mallet M, Duval M, De Lumley L, Hartmann O, Mechinaud F, Sirvent N, Orbach D, Doireau V, Boutard P, Dalle JH, Reguerre Y, Pautard B, Aubier F, Schneider P, Suc A, Couillaut G, Schmitt C; Pain task force of the SFCE.
Multicenter randomized trial of chewing gum for preventing oral mucositis in children receiving chemotherapy. Journal of Pediatric Hematology/Oncology. 2007;29(2):86-94.
Not applicable

Thomas X, Raffoux E, de Botton S, Pautas C, Arnaud P, de Revel T, Reman O, Terre C, Corront B, Gardin C, Le Q-H, Quesnel B, Cordonnier C, Bourhis J-H, Elhamri M, Fenaux P, Preudhomme C, Michallet M, Castaigne S, Dombret H. Effect of priming with granulocyte-macrophage colony-stimulating factor in younger adults with newly diagnosed acute myeloid leukemia: A trial by the Acute Leukemia French Association (ALFA) Group. Leukemia. 2007;21(3)(pp 453-461).
Adult data

Brethon B, Auvrignon A, Galambrun C, Yakouben K, Leblanc T, Bertrand Y, Leverger G, Baruchel A. Efficacy and tolerability of gemtuzumab ozogamicin (anti-CD33 monoclonal antibody, CMA-676, Mylotarg) in children with relapsed/refractory myeloid leukemia. BMC Cancer. 2006;6#172.
Not applicable

Sung WJ, Kim DH, Sohn SK, Kim JG, Baek JH, Jeon SB, Moon JH, Ahn BM, Lee KB. Phase II trial of amsacrine plus intermediate-dose ara-C (IDAC) with or without etoposide as salvage therapy for refractory or relapsed acute leukemia. Japanese Journal of Clinical Oncology. 2005;35(10):612-616.
Adult data

Spunt SL, Walsh MF, Krasin MJ, Helton KJ, Billups CA, Cain AM, Pappo AS. Brain metastases of malignant germ cell tumors in children and adolescents.
Cancer. 2004;101(3):620-626.
Not applicable

Langebrake C, Reinhardt D, Ritter J. Minimising the long-term adverse effects of childhood leukaemia therapy. Drug Safety. 2002;25(15):1057-1077.
Not applicable

Pellier I. Suivi a domicile des enfants sous chimiothérapie. Médecine Thérapeutique Pédiatrie. 2002;5(3):138-144.
Review article

Aksoylar S, Akman SA, Ozgenc F, Kansoy S. Comparison of tropisetron and granisetron in the control of nausea and vomiting in children receiving combined cancer chemotherapy. Pediatric Hematology and Oncology. 2001;18(6):397-406.
Results not reported per individual antineoplastic agents

Coppes MJ, Yanofsky R, Pritchard S, Leclerc J-M, Howard DR, Perrotta M, Keays S, Pyesmany A, Dempsey E, Pratt C.B. Safety, tolerability, antiemetic efficacy, and pharmacokinetics of oral dolasetron mesylate in pediatric cancer patients receiving moderately to highly emetogenic chemotherapy. Journal of Pediatric Hematology/Oncology. 1999;21(4):274-283.

Not applicable; not extensively referenced

Abrahamov A, Mechoulam R. An efficient new cannabinoid antiemetic in pediatric oncology. Life Sciences. 1995;56:23-24.

Specific details not reported

Ries F., Dicato M.A. Emesis control in hematological-oncology. Leukemia and Lymphoma. 1992;7(SUPPL. 2):83-89.

Review article

Deriu L., Nardelli S. Evolution of antiemetic treatment in hematologic patients. Leukemia and Lymphoma. 1992;7(SUPPL. 2):78-82.

Review article

Pellier I. Home follow-up of children under chemotherapy. Medecine Therapeutique Pediatrie. 2002;5(3):138-144.

Not applicable

Kofoed P.-E., Kamper J. Extrapyramidal reactions caused by antiemetics during cancer chemotherapy. Journal of Pediatrics. 1994;105(5):852-853.

Not applicable

Kell W.J., Burnett A.K., Chopra R., Yin J.A.L., Clark R.E., Rohatiner A., Culligan D., Hunter A., Prentice A.G., Milligan D.W. A feasibility study of simultaneous administration of gemtuzumab ozogamicin with intensive chemotherapy in induction and consolidation in younger patients with acute myeloid leukemia. Blood. 2003;102(13):4277-4283).

Not applicable

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

Ovid MEDLINE(R) 1950 to Present with Daily Update

Busulfan/	3301
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)")	850
exp Vomiting/	21339
3 and 2	2

Yen CC, Hsieh RK, Chiou TJ, Liu JH, Fang FS, Wang WS, Tung SL, Tzeng CH, Chen PM. Navoban (tropisetron, ICS 205-930) and dexamethasone combination in the prevention of vomiting for patients receiving preconditioning high-dose chemotherapy before marrow transplantation. Japanese Journal of Clinical Oncology. 1998;28(2):129-33.

Pediatric data combined with adult data

Hirabayashi N, Goto S, Morishima Y, Sao H, Matsuyama T, Kodera Y, Yamada H, Horibe K, Yano K, Kojima H, Ogura M, Tanimoto M, Morishita Y, Yazaki M, Utsumi M, Nagata K, Kato Y, Naoe T, Saito H. Efficacy of granisetron, a 5-HT3 antagonist, in the prevention of nausea and vomiting induced by conditioning for hematopoietic stem cell transplantation. Rinsho Ketsueki - Japanese Journal of Clinical Hematology. 1998; 39(1):21-6.

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

Caselli D, Ziino O, Bartoli A, Santangelo G, Vanadia F, Arico M. Continuous intravenous infusion of lorazepam as seizure prophylaxis in children treated with high-dose busulfan. Bone Marrow Transplantation. 2008;42(2):135-136.

No incidence data provided

Huang YH, He X-P, Xu K-L, Li D-P, Li B-L, Ji Y-H, Sun H-Y, Pan X-Y. Short-term and long-term toxicity of alkylating-agent-based conditioning regimens in hematopoietic stem cell transplantation. Journal of Clinical Rehabilitative Tissue Engineering Research. 2007;11(7):1382-1385.

Pediatric data combined with adult data

Gandemer V, Deley M-CL, Dollfus C, Auvrignon A, Bonnaure-Mallet M, Duval M, Lumley LD, Hartmann O, Mechinaud F, Sirvent N, Orbach D, Doireau V, Boutard P, Dalle J-H, Reguerre Y, Pautard B, Aubier F, Schneider P, Suc A, Couillaut G, Schmitt C. Multicenter randomized trial of chewing gum for preventing oral mucositis in children receiving chemotherapy. Journal of Pediatric Hematology/Oncology. 2007;29(2):86-94.

Not applicable

Sung KW, Yoo KH, Cho EJ, Koo HH, Lim DH, Shin HJ, Ahn SD, Ra YS, Choi ES, Ghim TT. High-dose chemotherapy and autologous stem cell rescue in children with newly diagnosed high-risk or relapsed medulloblastoma or supratentorial primitive neuroectodermal tumor. Pediatric Blood & Cancer. 2006;48(4):408-415.

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

Lee JH, Kwon BS, Ha IS, Cheong HI, Moon KC, Ahn HS, Choi Y. Nephrotic syndrome in a child after umbilical-cord-blood transplantation. Pediatric Nephrology. 2006;21(9):1312-1317.

Not applicable

Ek ETH, Choong PFM. The role of high-dose therapy and autologous stem cell transplantation for pediatric bone and soft tissue sarcomas. Expert Review of Anticancer Therapy. 2006;6(2):225-237.

Review article

Gharib MI, Bulley SR, Doyle JJ, Wynn RF. Venous occlusive disease in children. Thrombosis Research. 2006;118(1):27-38.

Not applicable

Gururangan S, Petros WP, Poussaint TY, Hancock ML, Phillips PC, Friedman HS, Bomgaars L, Blaney SM, Kun LE, Boyett JM. Phase I trial of intrathecal Spartaject Busulfan in children with neoplastic meningitis: A Pediatric Brain Tumor Consortium study (PBTC-004). Clinical Cancer Research. 2006;12(5):1540-1546.

Not applicable

Kletzel M, Jacobsohn D, Duerst R. Pharmacokinetics of a test dose of Intravenous busulfan guide dose modifications to achieve an optimal area under the curve of a single daily dose of intravenous busulfan in children undergoing a reduced-intensity conditioning regimen with hematopoietic stem cell transplantation. Biology of Blood and Marrow Transplantation. 2006;12(4):472-479.

Specific details not reported

Wang J-W, Tang S-Q, Yang G, Gao X-N, Feng C, Yu F. High-dose chemotherapy with autologous peripheral blood stem cell support in children with malignant diseases. Chinese Journal of Cancer Research. 2005;17(4):288-290).

Incidence of diarrhea and vomiting grouped together

Resnick IB, Abdul HA, Shapira MY, Bitan M, Hershkovitz E, Schwartz A, Ben-Harush M, Or R, Slavin S, Kapelushnik J. Treatment of X-linked childhood cerebral adrenoleukodystrophy by the use of an allogeneic stem cell transplantation with reduced intensity conditioning regimen. Clinical Transplantation. 2005;19(6):840-847.

Specific details not reported

Valteau-Couanet D, Fillipini B, Benhamou E, Grill J, Kalifa C, Couanet D, Habrand JL, Hartmann O. High-dose busulfan and thiotepa followed by autologous stem cell transplantation (ASCT) In previously irradiated medulloblastoma patients: High toxicity and lack of efficacy. Bone Marrow Transplantation. 2005;36(11):939-945.

Not applicable

Cappelli C, Ragni G, De Pasquale MD, Gonfiantini M, Russo D, Clerico A. Tropisetron: Optimal dosage for children in prevention of chemotherapy-induced vomiting. Pediatric Blood and Cancer. 2005;45(1):48-53.

Not applicable

Zwaveling J, Bredius RGM, Cremers SCLM, Ball LM, Lankester AC, Teepe-Twiss IM, Egeler RM, den Hartigh J, Vossen JM. Intravenous busulfan in children prior to stem cell transplantation: Study of pharmacokinetics in association with early clinical outcome and toxicity. Bone Marrow Transplantation. 2005;35(1):17-23.

Not applicable

Tran H, Petropoulos D, Worth L, Mullen CA, Madden T, Andersson B, Choroszy M, Nguyen J, Webb SK, Chan KW. Pharmacokinetics and individualized dose adjustment of intravenous busulfan in children with advanced hematologic malignancies undergoing allogeneic stem cell transplantation. Biology of Blood and Marrow Transplantation. 2004;10(11):805-812.

Not applicable

Maschan AA, Trakhtman PE, Balashov DN, Shipicina IP, Skorobogatova EV, Skvortsova YV, Dyshlevaja ZM, Samochatova EV, Rumiantsev AG. Fludarabine, low-dose busulfan and antithymocyte globulin as conditioning for Fanconi anemia patients receiving bone marrow transplantation from HLA-compatible related donors. Bone Marrow Transplantation. 2004;34(4):305-307.

Not applicable

Saikia TK, Parikh PM, Tawde S, Amare-Kadam PS, Rajadhyaksha S. Allogeneic blood stem cell transplantation in chronic myeloid leukaemia-chronic phase following conditioning with busulphan and cyclophosphamide: A follow up report. National Medical Journal of India. 2004;17(2):71-73.

Pediatric data grouped with adult data

Del Toro G, Satwani P, Harrison L, Cheung Y-K, Brigid Bradley M, George D, Yamashiro DJ, Garvin J, Skerret D, Bessmertny O, Wolownik K, Wischhover C, van de Ven C, Cairo MS. A pilot study of reduced intensity conditioning and allogeneic stem cell transplantation from unrelated cord blood and matched family donors in children and adolescent recipients. Bone Marrow Transplantation. 2004;33(6):613-622.

Time course of vomiting observed unknown

Burke JM, Caron PC, Papadopoulos EB, Divgi CR, Sgouros G, Panageas KS, Finn RD, Larson SM, O'Reilly RJ, Scheinberg DA, Jurcic JG. Cytoreduction with iodine-131-anti-CD33 antibodies before bone marrow transplantation for advanced myeloid leukemias. Bone Marrow Transplantation. 2003;32(6):549-556.

Not applicable

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Not applicable

McCune JS, Gooley T, Gibbs JP, Sanders JE, Petersdorf EW, Appelbaum FR, Anasetti C, Risler L, Sultan D, Slattery JT. Busulfan concentration and graft rejection in pediatric patients undergoing hematopoietic stem cell transplantation. Bone Marrow Transplantation. 2002;30(3):167-173.
Not applicable

Chan KW, Mullen CA, Worth LL, Choroszy M, Koontz S, Tran H, Slopis J. Lorazepam for seizure prohylaxis during high-dose busulfan admistration. Bone Marrow Transplantation. 2002;29(12):963-965.
Not applicable

Lazala C, Saenger P. Pubertal gynecomastia. Journal of Pediatric Endocrinology and Metabolism. 2002;15(5):553-560.
Not applicable

Langmuir PB, Aplenc R, Lange BJ. Acute myeloid leukaemia in children. Best Practice and Research in Clinical Haematology. 2001;14(1):77-93.
Not applicable

Tran HT, Madden T, Petropoulos D, Worth LL, Felix EA, Sprigg-Saenz HA, Choroszy M, Danielson M, Przepiorka D, Chan K-W. Individualizing high-dose oral busulfan: Prospective dose adjustment in a pediatric population undergoing allogeneic stem cell transplantation for advanced hematologic malignancies. Bone Marrow Transplantation. 2000;26(5):463-470.
Not applicable

Diaz MA, Vicent MG, Madero L. High-dose busulfan/melphalan as conditioning for autologous PBPC transplantation in pediatric patients with solid tumors. Bone Marrow Transplantation. 1999;24(11):1157-1159.
Not applicable

Rosales F, Peylan-Ramu N, Cividalli G, Varadi G, Or R, Naparstek E, Slavin S, Nagler A. The role of thiotepa in allogeneic bone marrow transplantation for genetic diseases. Bone Marrow Transplantation. 1999;23(9):861-865.
Incidence of nausea and vomiting grouped with diarrhea

Nagler A, Finlander R, Or R., Naparstek E, Varadi G, Slavin S. The role of thiotepa in autologous bone marrow transplantation for acute leukemia. Leukemia Research. 1998;22(11):991-995.
Incidence of nausea and vomiting grouped with diarrhea - excluded

Matsuyama T, Kojima S, Kato K. Allogeneic bone marrow transplantation for childhood leukemia following a busulfan and melphalan preparative regimen. Bone Marrow Transplantation. 1998;22(1):21-26.
Not appliable

Grill J, Kalifa C, Doz F, Schoepfer C, Sainte-Rose C, Couanet D, Terrier-Lacombe MJ, Valteau-Couanet D, Hartmann O. A high-dose busulfan-thiotepa combination followed by autologous bone marrow transplantation in childhood recurrent ependymoma. A phase-II study. Pediatric Neurosurgery. 1996;25(1):7-12.
Not applicable

Brenner M, Krance R, Heslop HE, Santana V, Ihle J, Ribiero R, Roberts WM, Mahmoud H, Boyett J, Moen RC, Klingemann H-G. Clinical protocol: Assessment of the efficacy of purging by using gene marked autologous marrow transplantation for children with AML in first complete remission. Human Gene Therapy. 1994;5(4):481-499.
Not applicable

van Genderen PJJ, Michiels JJ. Primary thrombocythemia: Diagnosis, clinical manifestations and management. Annals of Hematology. 1993;67(2):57-62.
R**eview article**

Sullivan MJ, Abbott GD, Robinson BA. Ondansetron antiemetic therapy for chemotherapy and radiotherapy induced vomiting in children. New Zealand Medical Journal. 1992;105(942):369-371.
Previously reviewed

Ries F, Dicato MA. Emesis control in hematological-oncology. Leukemia and Lymphoma. 1992;7(SUPPL. 2):83-89.
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

Fraiser LH, Kanekal S, Kehrer JP. Cyclophosphamide toxicity: Characterising and avoiding the problem. Drugs. 1991;42(5):781-795.
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

clofarabine.tw.	101
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)")	22
exp vomiting/ or exp antiemetics/	130679
3 and 2	1

Verma D. O'Brien S. Thomas D. Faderl S. Koller C. Pierce S. Kebriaei P. Garcia-Manero G. Cortes J. Kantarjian H. Ravandi F. Therapy-related acute myelogenous leukemia and myelodysplastic syndrome in patients with acute lymphoblastic leukemia treated with the hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone regimens. Cancer. 115(1):101-6, 2009 Jan 1.
Not applicable

EMBASE 1980 to 2009 Week 51

exp clofarabine/	408
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>)	40
exp "nausea and vomiting"/ or exp vomiting/	127397
exp antiemetic agent/	96160
3 and 2	8
4 and 2	0
6 or 5	8

Absalon MJ, Smith FO. Treatment strategies for pediatric acute myeloid leukemia. Expert Opinion on Pharmacotherapy. 2009;10(1):57-79.
Specific details not reported

Atallah E, Cortes J, O'Brien S, Pierce S, Rios MB, Estey E, Markman M, Keating M, Freireich EJ, Kantarjian H. Establishment of baseline toxicity expectations with standard frontline chemotherapy in acute myelogenous leukemia. Blood. 2007;110(10):3547-3551.
Not applicable

Steinherz PG, Meyers PA, Steinherz LJ, Jeha S. Clofarabine induced durable complete remission in heavily pretreated adolescents with relapsed and refractory leukemia. Journal of Pediatric Hematology/Oncology. 2007;29(9):656-658.
Not applicable

Corey S.J. New agents in the treatment of childhood leukemias and myelodysplastic syndromes. Current Oncology Reports. 2005;7(6):399-405.
Not applicable

Coutre S.E. Clofarabine active in relapsed/refractory pediatric leukemia. Oncology Report. 2005;(SPRING):84.
Specific details not reported

Corey SJ, Elopre M, Weitman S, Rytting ME, Robinson LJ, Rumelhart S, Goldman FD. Complete remission following clofarabine treatment in refractory juvenile myelomonocytic leukemia. Journal of Pediatric Hematology/Oncology. 2005;27(3):166-168.
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

Smirnova IN. [Results of treatment of tonsillar tumors by olivomycin]. [Russian] Antibiotiki. 14(3):271-4, 1969.
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

Agarwal R, Dvorak CC, Stockerl-Goldstein KE, Johnston L, Srinivas S. High-dose chemotherapy followed by stem cell rescue for high-risk germ cell tumors: The Stanford experience. Bone Marrow Transplantation. 2009;43(7):547-552.
Specific details not reported

Vuillermet P, Cauliez B, Freger P, Vannier JP, Pellerin A, Kuhn J-M. Simultaneous suprasellar and pineal germ cell tumors in five late stage adolescents: Endocrinological studies and prolonged follow-up. Journal of Pediatric Endocrinology and Metabolism. 2008;21(12):1169-1178.
Adult data

Koharazawa H, Kanamori H, Sakai R, Hashimoto C, Takemura S, Hattori M, Taguchi J, Fujimaki K, Tomita N, Fujita H, Fujisawa S, Harano H, Ogawa K, Motomura S, Maruta A, Ishigatsubo Y. Long-term outcome of L86 and L97 protocols for adult acute lymphoblastic leukemia. Leukemia and Lymphoma. 2008;49(11):2133-2140.
Adolescent and adult data

Holthouse DJ, Dallas PB, Ford J, Fabian V, Murch AR, Watson M, Wong G, Bertram C, Egli S, Baker DL, Kees UR. Classic and desmoplastic medulloblastoma: Complete case reports and characterizations of two new cell lines. Neuropathology. 2009;29(4):398-409.
Not applicable

Polydorides AD, Perry A, Edgar MA. Large cell medulloblastoma with myogenic and melanotic differentiation: A case report with molecular analysis. Journal of Neuro-Oncology. 2008;88(2):193-197.
Not applicable

de Braganca KC, Packer RJ. Neurotoxicity of chemotherapeutic and biologic agents in children with cancer. Current Neurology and Neuroscience Reports. 2008;8(2):114-122).
Review article

Tokuda Y, Tajima T, Narabayashi M, Takeyama K, Watanabe T, Fukutomi T, Chou T, Sano M, Igarashi T, Sasaki Y, Ogura M, Miura S, Okamoto S-I, Ogita M, Kasai M, Kobayashi T, Fukuda H, Takashima S, Tobinai K. Phase III study to evaluate the use of high-dose chemotherapy as consolidation of treatment for high-risk postoperative breast cancer: Japan Clinical Oncology Group study, JCOG 9208. Cancer Science. 2008;99(1):145-151.
Adult data

Johnston DL, Keene DL, Lafay-Cousin L, Steinbok P, Sung L, Carret A-S., Crooks B, Strother D, Wilson B, Odame I, Eisenstat DD, Mpofu C, Zelcer S, Huang A, Bouffet E. Supratentorial primitive neuroectodermal tumors: A Canadian pediatric brain tumor consortium report. Journal of Neuro-Oncology. 2008;86(1):101-108.
Not applicable

Steinherz PG, Meyers PA, Steinherz LJ, Jeha S. Clofarabine induced durable complete remission in heavily pretreated adolescents with relapsed and refractory leukemia. Journal of Pediatric Hematology/Oncology. 2007;29(9):656-658.
Not applicable

Shamash J, Powles T, Ansell W, Stebbing J, Mutsvangwa K, Wilson P, Asterling S, Liu S, Wyatt P, Joel SP, Oliver RTD. GAMEC - A new intensive protocol for untreated poor prognosis and relapsed or refractory germ cell tumours. British Journal of Cancer. 2007;97(3):308-314.
Adolescent and adult data

Sung KW, Lee SH, Yoo KH, Jung HL, Cho EJ, Koo HH, Lee SK, Kim J, Lim DH, Suh YL, Kim DW. Tandem high-dose chemotherapy and autologous stem cell rescue in patients over 1 year of age with stage 4 neuroblastoma. Bone Marrow Transplantation. 2007;40(1):37-45.
Not specific to thiotepa; nausea and vomiting grouped with other side effects

Moore HCF, Green SJ, Gralow JR, Bearman SI, Lew D, Barlow WE, Hudis C, Wolff AC, Ingle JN, Chew HK, Elias AD, Livingston RB, Martino S. Intensive dose-dense compared with high-dose adjuvant chemotherapy for high-risk operable breast cancer: Southwest Oncology Group/Intergroup study 9623. Journal of Clinical Oncology. 2007;25(13):1677-1682.
Adult data

Sung KW, Yoo KH, Cho EJ, Koo HH, Lim DH, Shin HJ, Ahn SD, Ra YS, Choi ES, Ghim TT. High-dose chemotherapy and autologous stem cell rescue in children with newly diagnosed high-risk or relapsed medulloblastoma or supratentorial primitive neuroectodermal tumor. Pediatric Blood and Cancer. 2007;48(4):408-415.
Not specific to thiotepa

Bourne TD, Mandell JW, Matsumoto JA, Jane Jr. JA, Lopes MBS. Primary disseminated leptomeningeal oligodendroglioma with 1p deletion: Case report. Journal of Neurosurgery. 105 PEDIATRICS 2006;(Suppl.6):465-469.
Not applicable

Rodriguez V, Anderson PM, Litzow MR, Erlandson L, Trotz BA, Arndt CAS, Khan SP, Wiseman GA. Marrow irradiation with high-dose 153Samarium-EDTMP followed by chemotherapy and hematopoietic stem cell infusion for acute myelogenous leukemia. Leukemia and Lymphoma. 2006;47(8):1583-1592.
Not applicable

Thompson B, Salzman D, Steinhauer J, Lazenby AJ, Wilcox CM. Bone Marrow Transplantation. 2006;38(5):371-376).
Not applicable

Ek ETH, Choong PFM. The role of high-dose therapy and autologous stem cell transplantation for pediatric bone and soft tissue sarcomas. Expert Review of Anticancer Therapy. 2006;6(2):225-237.
Review article

Ruggiero A, Cefalo G, Garre ML, Massimino M, Colosimo C, Attinaa G, Lazzareschi I, Maurizi P, Ridola V, Mazzarella G, Caldarelli M, Di Rocco C, Madon E, Abate ME, Clerico A, Sandri A, Riccardi R. Phase II trial of temozolomide in children with recurrent high-grade glioma. Journal of Neuro-Oncology. 2006;77(1):89-94.
Not applicable

El Kababri M, Andre N, Carole C, Gentet JC, Lena G, Figarella-Branger D. Atypical teratoid rhabdoid tumor in a child with neurofibromatosis 1. Pediatric Blood and Cancer. 2006;46(2):267-268.
Not applicable

Papadopoulos KP, Noguera-Irizarry W, Wiebe L, Hesdorffer CS, Garvin J, Nichols GL, Vahdat LH, Lo KMS, Skerrett D, Bernstein D, Sharpe E, Savage DG. Pilot study of tandem high-dose chemotherapy and autologous stem cell transplantation with a novel combination of regimens in patients with poor risk lymphoma. Bone Marrow Transplantation. 2005;36(6):491-497.
Adolescent and adult data

Cipri S, Gangemi A, Cafarelli F, Messina G, Iacopino P, Al Sayyad S, Capua A, Comi M, Musitano A. Neuroendoscopic management of hydrocephalus secondary to midline and pineal lesions. Journal of Neurosurgical Sciences. 2005;49(3):97-106).
Not applicable

MacDonald TJ, Arenson EB, Ater J, Sposto R, Bevan HE, Bruner J, Deutsch M, Kurczynski E, Luerssen T, McGuire-Cullen P, O'Brien R, Shah N, Steinbok P, Strain J, Thomson J, Holmes E, Vezina G, Yates A, Phillips P, Packer R. Phase II study of high-dose chemotherapy before radiation in children with newly diagnosed high-grade astrocytoma: Final analysis of Children's Cancer Group Study 9933. Cancer. 2005;104(12):2862-2871.
Not applicable

Valteau-Couanet D, Fillipini B, Benhamou E, Grill J, Kalifa C, Couanet D, Habrand JL, Hartmann O. High-dose busulfan and thiotepa followed by autologous stem cell transplantation (ASCT) In previously irradiated medulloblastoma patients: High toxicity and lack of efficacy. Bone Marrow Transplantation. 2005;36(11):939-945.
Specific details not reported

Isaacs C, Slack R, Gehan E, Ballen K, Boccia R, Areman E, Kramer R, Hayes DF, Herscowitz H, Lippman M. A multicenter randomized clinical trial evaluating interleukin-2 activated hematopoietic stem cell transplantation and post-transplant IL-2 for high risk breast cancer patients. Breast Cancer Research and Treatment. 2005;93(2):125-134.
Adult data

Cappelli C, Ragni G, De Pasquale MD, Gonfiantini M, Russo D, Clerico A.
Tropisetron: Optimal dosage for children in prevention of chemotherapy-induced vomiting. Pediatric Blood and Cancer. 2005;45(1):48-53.
Not applicable

Herrlinger U, Steinbrecher A, Rieger J, Hau P, Kortmann R-D, Meyermann R, Schabet M, Bamberg M, Dichgans J, Bogdahn U, Weller M. Adult medulloblastoma: Prognostic factors and response to therapy at diagnosis and at relapse. Journal of Neurology. 2005;252(3):291-299.
Adult data

Lotz J-P, Bui B, Gomez F, Theodore C, Caty A, Fizazi K, Gravis G, Delva R, Peny J, Viens P, Duclos B, De Revel T, Cure H, Gligorov J, Guillemaut S, Segura C, Provent S, Droz J-P, Culine S, Biron P. Sequential high-dose chemotherapy protocol for relapsed poor prognosis germ cell tumors combining two mobilization and cytoreductive treatments followed by three high-dose chemotherapy regimens supported by autologous stem cell transplantation. Results of the phase II multicentric TAXIF trial. Annals of Oncology. 2005;16(3):411-418.
Adolescent and adult data

Tran H, Petropoulos D, Worth L, Mullen CA, Madden T, Andersson B, Choroszy M, Nguyen J, Webb SK, Chan KW. Pharmacokinetics and individualized dose adjustment of intravenous busulfan in children with advanced hematologic malignancies undergoing allogeneic stem cell transplantation. Biology of Blood and Marrow Transplantation. 2004;10(11):805-812.
Specific details not reported

Novitzky N, Thomas V, Abrahams L, Du Toit C, McDonald A. Increasing dose intensity of anthracycline antibiotics improves outcome in patients with acute myelogenous leukemia. American Journal of Hematology. 2004;76(4):319-329.
Adult data

Slavc I, Schuller E, Falger J, Gunes M, Pillwein K, Czech T, Dietrich W, Rossler K, Dieckmann K, Prayer D, Hainfellner J. Feasibility of long-term intraventricular therapy with mafosfamide (n = 26) and etoposide (n = 11): Experience in 26 children with disseminated malignant brain tumors. Journal of Neuro-Oncology. 2003;64(3):239-247.
Not applicable

Begemann M, Lyden D, Rosenblum MK, Lis E, Wolden S, Antunes NL, Dunkel IJ. Primary leptomeningeal primitive neuroectodermal tumor. Journal of Neuro-Oncology. 2003;63(3):299-303.
Not applicable

Postovsky S, Ben Arush MW, Elhasid R, Davidson S, Leshanski L, Vlodavsky E, Guilburd JN, Amikam D. A novel case of a CAT to AAT transversion in codon 179 of the p53 gene in a supratentorial primitive neuroectodermal tumor harbored by a young girl: Case report and review of the literature. Oncology. 2003;65(1):46-51.
Not applicable

Sung KW, Yoo KH, Chung EH, Jung HL, Koo HH, Shin HJ, Lee SK, Lim DH, Kim DW, Park HK, Cho EJ, Kim SW. Successive double high-dose chemotherapy with peripheral blood stem cell rescue collected during a single leukapheresis round in patients with high-risk pediatric solid tumors: A pilot study in a single center. Bone Marrow Transplantation. 2003;31(6):447-452.
Specific details not reported

Matsubara H, Makimoto A, Higa T, Kawamoto H, Takayama J, Ohira M, Yokoyama R, Beppu Y, Takaue Y. Possible benefits of high-dose chemotherapy as intensive consolidation in patients with high-risk rhabdomyosarcoma who achieve complete remission with conventional chemotherapy. Pediatric Hematology and Oncology. 2003;20(3):201-210.
Specific details not reported

Kremens B, Wieland R, Reinhard H, Neubert D, Beck JD, Klingebiel T, Bornfeld N, Havers W. High-dose chemotherapy with autologous stem cell rescue in children with retinoblastoma. Bone Marrow Transplantation. 2003;31(4):281-284.
Specific details not reported

Wassmann B, Pfeifer H, Scheuring U, Klein SA, Gokbuget N, Binckebanck A, Martin H, Gschaidmeier H, Hoelzer D, Ottmann OG. Therapy with imatinib mesylate (Glivec) preceding allogeneic stem cell transplantation (SCT) in relapsed or refractory Philadelphia-positive acute lymphoblastic leukemia (Ph+ALL). Leukemia. 2002;16(12):2358-2365.

Specific details not reported

Sandri A, Sardi N, Besenzon L, Cordero Di Montezemolo L, Ricardi U, Papalia F, Madon E. Brain stem tumors in pediatric age. Italian Journal of Pediatrics. 2002;28(1):33-40.

Not applicable

Bunjes D. ^{188}Re-labeled anti-CD66 monoclonal antibody in stem cell transplantation for patients with high-risk acute myeloid leukemia. Leukemia and Lymphoma. 2002;43(11):2125-2131).

Adult data

Chan KW, Mullen CA, Worth LL, Choroszy M, Koontz S, Tran H, Slopis J. Lorazepam for seizure prohylaxis during high-dose busulfan admistration. Bone Marrow Transplantation. 2002;29(12):963-965.

Specific details not reported

Nagler A, Ackerstein A, Or R, Naparstek E, Slavin S. Adoptive immunotherapy with haploidentical allogeneic peripheral blood lymphocytes following autologous bone marrow transplantation. Experimental Hematology. 2000;28(11):1225-1231.

Not appliable

Tran HT, Madden T, Petropoulos D, Worth LL, Felix EA, Sprigg-Saenz HA, Choroszy M, Danielson M, Przepiorka D, Chan K-W. Individualizing high-dose oral busulfan: Prospective dose adjustment in a pediatric population undergoing allogeneic stem cell transplantation for advanced hematologic malignancies. Bone Marrow Transplantation. 2000;26(5):463-470.

Not applicable

Rosales F, Peylan-Ramu N, Cividalli G, Varadi G, Or R, Naparstek E, Slavin S, Nagler A. The role of thiotepa in allogeneic bone marrow transplantation for genetic diseases. Bone Marrow Transplantation. 1999;23(9):861-865.

Incidence of nausea and vomiting was grouped with incidence of diarrhea

Papadopoulos KP, Garvin JH, Fetell M, Vahdat LT, Garrett TJ, Savage DG, Balmaceda C, Bruce J, Sisti M, Isaacson S, De Lapaz R, Hawks R, Bagiella E, Antman KH, Hesdorffer C.S. High-dose thiotepa and etoposide-based regimens with autologous hematopoietic support for high-risk or recurrent CNS tumors in children and adults. Bone Marrow Transplantation. 1998;22(7):661-667.

Pediatric data combined with adult data

Nagler A, Finlander R, Or R, Naparstek E, Varadi G, Slavin S. The role of thiotepa in autologous bone marrow transplantation for acute leukemia. Leukemia Research. 1998;22(11):991-995.

Incidence of nausea and vomiting was grouped with incidence of diarrhea

Mason WP, Grovas A, Halpern S, Dunkel IJ, Garvin J, Heller G, Rosenblum M, Gardner S, Lyden D, Sands S, Puccetti D, Lindsley K, Merchant TE, O'Malley B, Bayer L, Petriccione MM, Allen J, Finlay JL. Intensive chemotherapy and bone marrow rescue for young children with newly diagnosed malignant brain tumors. Journal of Clinical Oncology. 1998;16(1):210-221.

Specific details not reported

Chan KW, Petropoulos D, Choroszy M, Herzog C, Jaffe N, Ater J, Korbling M. High-dose sequential chemotherapy and autologous stem cell reinfusion in advanced pediatric solid tumors. Bone Marrow Transplantation. 1997;20(12):1039-1043.

Specific details not reported

Grill J, Kalifa C, Doz F, Schoepfer C, Sainte-Rose C, Couanet D, Terrier-Lacombe MJ, Valteau-Couanet D, Hartmann O. A high-dose busulfan-thiotepa combination followed by autologous bone marrow transplantation in childhood recurrent ependymoma. A phase-II study. Pediatric Neurosurgery. 1996;25(1):7-12.

Specific details not provided

Berard CM, Mahoney CD. Cost-reducing treatment algorithms for antineoplastic drug-induced nausea and vomiting. American Journal of Health-System Pharmacy. 1995;52(17):1879-1885.
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Kim S, Chatelut E, Kim JC, Howell SB, Cates C, Kormanik PA, Chamberlain MC. Extended CSF cytarabine exposure following intrathecal administration of DTC 101. Journal of Clinical Oncology. 1993;11(11):2186-2193.
Not applicable

Heideman RL, Douglass EC, Krance RA, Fontanesi J, Langston JA, Sanford RA, Kovnar EH, Ochs J, Kuttesch J, Jenkins JJ, Fairclough DL, Kun LE High-dose chemotherapy and autologous bone marrow rescue followed by interstitial and external-beam radiotherapy in newly diagnosed pediatric malignant gliomas. Journal of Clinical Oncology. 1993;11(8):1458-1465.
Specific details not reported

Donfrancesco A, Deb G, Angioni A, Maurizio C, Cozza R, Jenkner A, Landolfo A, Boglino C, Helson L. D-CECaT: A breakthrough for patients with neuroblastoma. Anti-Cancer Drugs. 1993;4(3):317-321.
Specific details not reported

Moormeier JA, Williams SF, Kaminer LS, Ellis ED, Garner M, Farah Weichselbaum RRR, Bitran JD. Autologous bone marrow transplantation followed by involved field radiotherapy in patients with relapsed or refractory Hodgkin's disease. Leukemia and Lymphoma. 1991;5(4):243-248.
Adolescent and adult data

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

Ovid MEDLINE(R) 1950 to September Week 2 2009

exp Etoposide/	12495
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)")	2588
exp Vomiting/	21430
3 and 2	14

Sung WJ, Kim DH, Sohn SK, Kim JG, Baek JH, Jeon SB, Moon JH, Ahn BM, Lee KB. Phase II trial of amsacrine plus intermediate-dose Ara-C (IDAC) with or without etoposide as salvage therapy for refractory or relapsed acute leukemia. Japanese Journal of Clinical Oncology. 2005;35(10):612-6.
Adolescent and adult data

Fulda S, Fichtner I, Hero B, Berthold F, Preclinical and clinical aspects on the use of amifostine as chemoprotector in neuroblastoma patients. Medical & Pediatric Oncology. 2001;36(1):199-202.
Not applicable

Guenther PP, Huebner A, Sobottka SB, Neumeister V, Weissbach G, Todt H, Parwaresch R. Temporary response of localized intracranial mast cell sarcoma to combination chemotherapy. Journal of Pediatric Hematology/Oncology. 2001;23(2):134-8.
Not applicable

Renner S, Krumpelmann S, Bruchelt G, Wiesinger H, Niethammer D, Klingebiel T. Effect of amifostine on neuroblastoma during high dose chemotherapy: in vivo and in vitro investigations. Anticancer Research. 2000;20(6B):4531-8.
Not applicable

Alvarado Ibarra ML, Borbolla Escoboza JR, Lopez-Hernandez MA, Gonzalez-Avante CM, FloresChapa JD, Trueba Christy E, Anaya Cuellar I. Neutrophil recovery time and adverse side effects in acute leukemia patients treated with intensive chemotherapy and concomitant G or GM-CSF. Revista de Investigacion Clinica. 1999;51(2):77-80.

Not applicable

Tfayli A, Hentschel P, Madajewicz S, Manzione J, Chowhan N, Davis R, Roche P, Iliya A, Roque C, Meek A, Shady M. Toxicities related to intraarterial infusion of cisplatin and etoposide in patients with brain tumors. Journal of Neuro-Oncology. 1999;42(1):73-7.

Adolscent and adult data

Buckner JC, Peethambaram PP, Smithson WA, Groover RV, Schomberg PJ, Kimmel DW, Raffel C, O'Fallon JR, Neglia J, Shaw EG. Phase II trial of primary chemotherapy followed by reduced-dose radiation for CNS germ cell tumors. Journal of Clinical Oncology. 1999;17(3):933-40.

Not applicable

Yamasaki T, Konishi S, Kagawa T, Nagai H, Nagao S, Moritake K. The efficacy of granisetron as a prophylactic anti-emetic agent used in conjunction with MCNU and VP16 chemotherapeutic regimens in the management of a pediatric case of hypothalamic anaplastic astrocytoma. Gan to Kagaku Ryoho [Japanese Journal of Cancer & Chemotherapy]. 1995;22(10):1397-402.

Article not in English/French (Japanese)

Falkson G, Chasen MR, Falkson HC. Ifosfamide and mesna in combination with other cytostatic drugs in the treatment of patients with advanced cancer. Investigational New Drugs. 1990;8(2):215-9.

Adolscent and adult data

Wolff SN, Johnson DH, Hainsworth JD, Greco FA. High-dose VP-16-213 monotherapy for refractory germinal malignancies: a phase II study. Journal of Clinical Oncology. 1984;2(4):271-4.

Adolscent and adult data

Melia WM, Westaby D, Williams R. Diamminodichloride platinum (cis-platinum) in the treatment of hepatocellular carcinoma. Clinical Oncology. 1981;7(4):275-80.

Adolscent and adult data

Van Echo DA, Wiernik PH, Aisner J. High-dose VP 16-213 (NSC 141540) for the treatment of patients with previously treated acute leukemia. Cancer Clinical Trials. 1980;3(4):325-8.

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

Griffin TC, Weitzman S, Weinstein H, Chang M, Cairo M, Hutchison R, Shiramizu B, Wiley J, Woods D, Barnich M, Gross TG. A study of rituximab and ifosfamide, carboplatin, and etoposide chemotherapy in children with recurrent/refractory B-cell (CD20+) non-Hodgkin lymphoma and mature B-cell acute lymphoblastic leukemia: A report from the Children's Oncology Group. Pediatric Blood and Cancer. 2009;52(2):177-181.
Specific details not reported

Daw N.C., Gregornik D., Rodman J., Marina N., Wu J., Kun L.E., Jenkins J.J., McPherson V., Wilimas J., Jones D.P. Renal function after ifosfamide, carboplatin and etoposide (ICE) chemotherapy, nephrectomy and radiotherapy in children with wilms tumour. European Journal of Cancer. 45(1)(pp 99-106), 2009.
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

Pearson AD, Pinkerton CR, Lewis IJ, Imeson J, Ellershaw C, Machin D. High-dose rapid and standard induction chemotherapy for patients aged over 1 year with stage 4 neuroblastoma: a randomised trial. The Lancet Oncology. 2008;9(3):247-256.
Specific details not reported

Ozkaynak MF, Sahdev I, Gross TG, Levine JE, Cheerva AC, Richards MK, Rozans MK, Shaw PJ, Kadota RP. A pilot study of addition of amifostine to melphalan, carboplatin, etoposide, and cyclophosphamide with autologous hematopoietic stem cell transplantation in pediatric solid tumors - A pediatric blood and marrow transplant consortium study. Journal of Pediatric Hematology/Oncology. 2008;30(3):204-209.
Specific details not reported

de Braganca KC, Packer RJ. Neurotoxicity of chemotherapeutic and biologic agents in children with cancer. Current Neurology and Neuroscience Reports. 2008;8(2):114-122.
Review article

Miser JS, Goldsby RE, Chen Z, Krailo MD, Tarbell NJ, Link MP, Fryer CJH, Pritchard DJ, Gebhardt MC, Dickman PS, Perlman EJ, Meyers PA, Donaldson SS, Moore SG, Rausen AR, Vietti TJ, Grier HE. Treatment of metastatic Ewing sarcoma/primitive neuroectodermal tumor of bone: Evaluation of increasing the dose intensity of chemotherapy - A report from the Children's Oncology Group. Pediatric Blood and Cancer. 2007;49(7):894-900.
Not applicable

Pein F, Pinkerton R, Berthaud P, Pritchard-Jones K, Dick G, Vassal G. Dose finding study of oral PSC 833 combined with weekly intravenous etoposide in children with relapsed or refractory solid tumours. European Journal of Cancer. 2007;43(14):2074-2081.
Not applicable

Huang Y-H, He X-P, Xu K-L, Li D-P, Li B-L, Ji Y-H, Sun H-Y, Pan X-Y. Short-term and long-term toxicity of alkylating-agent-based conditioning regimens in hematopoietic stem cell transplantation. Journal of Clinical Rehabilitative Tissue Engineering Research. 2007;11(7):1382-1385.
Pediatric and adult data combined

Yokoi K, Akiyama M, Yanagisawa T, Takahashi-Fujigasaki J, Yokokawa Y, Mikami-Terao Y, Fukuoka K, Fujisawa K, Nakazaki H, Oi S, Eto Y, Yamada H. Sequential analysis of cadherin expression in a 4-year-old girl with intracranial ependymoma. Child's Nervous System. 2007;23(2):237-242.
Not applicable

Seibel NL, Krailo M, Chen Z, Healey J, Breitfeld PP, Drachtman R, Greffe B, Nachman J, Nadel H, Sato JK, Meyers PA, Reaman GH. Upfront window trial of topotecan in previously untreated children and adolescents with poor prognosis metastatic osteosarcoma: Children's Cancer Group (CCG) 7943. Cancer. 2007;109(8):1646-1653.
Specific details not reported

Juergens C, Weston C, Lewis I, Whelan J, Paulussen M, Oberlin O, Michon J, Zoubek A, Juergens H, Craft A. Safety assessment of intensive induction with vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) in the treatment of ewing tumors in the EURO-E.W.I.N.G. 99 Clinical Trial. Pediatric Blood and Cancer. 2006;47(1):22-29.
Specific details not reported

Nathan PC, Tomlinson G, Dupuis LL, Greenberg ML, Ota S, Bartels U, Feldman BM. A pilot study of ondansetron plus metopimazine vs. ondansetron monotherapy in children receiving highly emetogenic chemotherapy: A Bayesian randomized serial N-of-1 trials design. Support Care Cancer. 2006 Mar;14(3):268-76.
Specific details not reported

McTiernan A, Meyer T, Michelagnoli MP, Lewis I, Whelan JS. A phase I/II study of doxorubicin, ifosfamide, etoposide and interval methotrexate in patients with poor prognosis osteosarcoma. Pediatric Blood and Cancer. 2006;46(3):345-350.
Adolescent and adult data

Wimmer RS, Chauvenet AR, London WB, Villaluna D, De Alarcon PA, Schwartz CL.
APE chemotherapy for children with relapsed Hodgkin disease: A pediatric oncology group trial. Pediatric Blood and Cancer. 2006;46(3):320-324.
Specific details not reported

Valteau-Couanet D, Michon J, Boneu A, Rodary C, Perel Y, Bergeron C, Rubie H, Coze C, Plantaz D, Bernard F, Chastagner P, Bouzy J, Hartmann O. Results of induction chemotherapy in children older than 1 year with a stage 4 neuroblastoma treated with the NB 97 French Society of Pediatric Oncology (SFOP) protocol. Journal of Clinical Oncology. 2005;23(3):532-540.
Grouped anorexia data with vomiting

Khan HI, Ijaz I. Childhood Hodgkin's lymphoma: Treatment, outcome and complications of 44 cases. Medical Forum Monthly. 2005;16(4):3-6.
Adolescent and adult data

Wang J-W, Tang S-Q, Yang G, Gao X-N, Feng C, Yu F. High-dose chemotherapy with autologous peripheral blood stem cell support in children with malignant diseases. Chinese Journal of Cancer Research. 2005;17(4):288-290.
Grouped diarrhea data with vomiting

Levy AS. Brain Tumors in Children: Evaluation and Management. Current Problems in Pediatric and Adolescent Health Care. 2005;35(6):230-245.
Review article

Sato N, Furukawa T, Kuroha T, Hashimoto S, Masuko M, Takahashi H, Yano T, Abe T, Fuse I, Koike T, Kishi K, Aizawa Y. High-dose cytosine arabinoside and etoposide with total body irradiation as a preparatory regimen for allogeneic hematopoietic stem-cell transplantation in patients with acute lymphoblastic leukemia. Bone Marrow Transplantation. 2004;34(4):299-303.
Pediatric and adult data combined

Aoyama H, Shirato H, Ikeda J, Fujieda K, Miyasaka K, Sawamura Y. Induction chemotherapy followed by low-dose involved-field radiotherapy for intracranial germ cell tumors. Journal of Clinical Oncology. 2002;20(3):857-865.
Specific details not reported

Stuart MJ, Chao NS, Horning SJ, Wong RM, Negrin RS, Johnston LJ, Shizuru JA, Long GD, Blume KG, Stockerl-Goldstein KE. Efficacy and toxicity of a CCNU-containing high-dose chemotherapy regimen followed by autologous hematopoietic cell transplantation in relapsed or refractory Hodgkin's disease. Biology of Blood and Marrow Transplantation. 2001;7(10):552-560.
Pediatric and adult data combined

Fouladi M, Stempak D, Gammon J, Klein J, Grant R, Greenberg ML, Koren G, Baruchel S. Phase I trial of a twice-daily regimen of amifostine with ifosfamide, carboplatin, and etoposide chemotherapy in children with refractory carcinoma. Cancer. 2001;92(4):914-923.

Not applicable

Stockhorst U, Spennes-Saleh S, Korholz D, Gobel U, Schneider ME, Steingruber H-J, Klosterhalfen S. Anticipatory symptoms and anticipatory immune responses in pediatric cancer patients receiving chemotherapy: Features of a classically conditioned response?. Brain, Behavior, and Immunity. 2000;14(3):198-218.

Specific details not reported

Holdsworth MT, Adams VR, Raisch DW, Wood JG, Winter SS. Computerized system for outcomes-based antiemetic therapy in children. Annals of Pharmacotherapy. 2000;34(10):1101-1108.

Specific details not reported

Uluoglu C, Oguz A, Timlioglu O, Biberoglu G, Hasanoglu A. Intermediate dose of methotrexate toxicity in non-Hodgkin lymphoma. Vascular Pharmacology. 1999;32(2):215-218.

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

Renner S, Krumpelmann S, Bruchelt G, Wiesinger H, Niethammer D, Klingebiel T. Effect of amifostine on neuroblastoma during high dose chemotherapy: in vivo and in vitro investigations. Anticancer Research. 2000;20(6B):4531-8.

Not applicable

Capelli D, Santini G, De Souza C, Poloni A, Marino G, Montanari M, Lucesole M, Brunori M, Massidda D, Offidani M, Leoni P, Olivieri A. Amifostine can reduce mucosal damage after high-dose melphalan conditioning for peripheral blood progenitor cellautotransplant: a retrospective study. British Journal of Haematology. 2000;110(2):300-7.

Adult data

Yen CC, Hsieh RK, Chiou TJ, Liu JH, Fang FS, Wang WS, Tung SL, Tzeng CH, Chen PM. Navoban (tropisetron, ICS 205-930) and dexamethasone combination in the prevention of vomiting for patients receiving preconditioning high-dose chemotherapy before marrow transplantation. Japanese Journal of Clinical Oncology. 1998;28(2):129-33.

Specific details not reported

Hirabayashi N. Goto S. Morishima Y. Sao H. Matsuyama T. Kodera Y. Yamada H. Horibe K, Yano K, Kojima H, Ogura M, Tanimoto M, Morishita Y, Yazaki M, Utsumi M, Nagata K, Kato Y, Naoe T, Saito H. Efficacy of granisetron, a 5-HT3 antagonist, in the prevention of nausea and vomiting induced by conditioning for hematopoietic stem cell transplantation. Rinsho Ketsueki - Japanese Journal of Clinical Hematology. 1998;39(1):21-6.

Article not in English/French (Japanese)

Bodey GP, Gottlieb JA, Burgess MA, Alexanian R. Clinical evaluation of Asaley. Medical & Pediatric Oncology. 1977;3(4):365-71.

Adult data

Smirnova IN. Results of treatment of tonsillar tumors by olivomycin. Antibiotiki. 1969;14(3):271-4.
Article not in English/French (Russian)

Samuels ML, Howe CD. Cyclophosphamide in the management of Ewing's sarcoma. Cancer. 1967;20(6):961-6.
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

Kadota RP, Mahoney DH, Doyle J, Duerst R, Friedman H, Holmes E, Kun L, Zhou T, Pollack IF. Dose intensive melphalan and cyclophosphamide with autologous hematopoietic stem cells for recurrent medulloblastoma or germinoma. Pediatric Blood and Cancer. 2008;51(5):675-678.
Not applicable

Bhatla D, Davies SM, Shenoy S, Harris RE, Crockett M, Shoultz L, Smolarek T, Bleesing J, Hansen M, Jodele S, Jordan M, Filipovich AH, Mehta PA. Reduced-intensity conditioning is effective and safe for transplantation of patients with Shwachman-Diamond syndrome. Bone Marrow Transplantation. 2008;42(3):159-165.
Not applicable

Ozkaynak MF, Sahdev I, Gross TG, Levine JE, Cheerva AC, Richards MK, Rozans MK, Shaw PJ, Kadota RP. A pilot study of addition of amifostine to melphalan, carboplatin, etoposide, and cyclophosphamide with autologous hematopoietic stem cell transplantation in pediatric solid tumors - A pediatric blood and marrow transplant consortium study. Journal of Pediatric Hematology/Oncology. 2008;30(3):204-209.
Not applicable

Gandemer V, Deley M-CL, Dollfus C, Auvrignon A, Bonnaure-Mallet M, Duval M, Lumley LD, Hartmann O, Mechinaud F, Sirvent N, Orbach D, Doireau V, Boutard P, Dalle J-H, Reguerre Y, Pautard B, Aubier F, Schneider P, Suc A, Couillaut G, Schmitt C. Multicenter randomized trial of chewing gum for preventing oral mucositis in children receiving chemotherapy. Journal of Pediatric Hematology/Oncology. 2007;29(2):86-94.
Not applicable

Sung KW, Yoo KH, Cho EJ, Koo HH, Lim DH, Shin HJ, Ahn SD, Ra YS, Choi ES, Ghim TT. High-dose chemotherapy and autologous stem cell rescue in children with newly diagnosed high-risk or relapsed medulloblastoma or supratentorial primitive neuroectodermal tumor. Pediatric Blood and Cancer. 2007;48(4):408-415.
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

Ek ETH, Choong PFM. The role of high-dose therapy and autologous stem cell transplantation for pediatric bone and soft tissue sarcomas. Expert Review of Anticancer Therapy. 2006;6(2):225-237.
Review article

Wang J-W, Tang S-Q, Yang G, Gao X-N, Feng C, Yu F. High-dose chemotherapy with autologous peripheral blood stem cell support in children with malignant diseases. Chinese Journal of Cancer Research. 2005;17(4):288-290.
Not applicable

Cappelli C, Ragni G, De Pasquale MD, Gonfiantini M, Russo D, Clerico A. Tropisetron: Optimal dosage for children in prevention of chemotherapy-induced vomiting. Pediatric Blood and Cancer. 2005;45(1):48-53.
Not applicable

Nieto Y, Shpall EJ, Bearman SI, McSweeney PA, Cagnoni PJ, Matthes S, Gustafson D, Long M, Baron AE, Jones RB. Phase I and pharmacokinetic study of docetaxel combined with melphalan and carboplatin, with autologous hematopoietic progenitor cell support, in patients with advanced refractory malignancies. Biology of Blood and Marrow Transplantation. 2005;11(4):297-306.
Specific details not reported

Zwaveling J, Bredius RGM, Cremers SCLM, Ball LM, Lankester AC, Teepe-Twiss IM, Egeler RM, den Hartigh J, Vossen JM. Intravenous busulfan in children prior to stem cell transplantation: Study of pharmacokinetics in association with early clinical outcome and toxicity. Bone Marrow Transplantation. 2005;35(1):17-23.
Not applicable

Hotte SJ, Smith AM, Bramwell VHC, Howson-Jan K. High-dose chemotherapy followed by peripheral and/or bone marrow stem cell transplant in patients with advanced sarcoma: Experience of a Canadian Centre. Sarcoma. 2004;8(2-3):63-69.
Not applicable

Delaloye J, Merlani G, Petignat C, Wenger A, Zaman K, Monnerat C, Matzinger O, Beck Popovic M, Vuichard P, Ketterer N, Tarr PE. Nosocomial nontyphoidal salmonellosis after antineoplastic chemotherapy: Reactivation of asymptomatic colonization?. European Journal of Clinical Microbiology and Infectious Diseases. 2004;23(10):751-758.
Specific details not reported

Matsubara H, Makimoto A, Higa T, Kawamoto H, Takayama J, Ohira M, Yokoyama R, Beppu Y, Takaue Y. Possible benefits of high-dose chemotherapy as intensive consolidation in patients with high-risk rhabdomyosarcoma who achieve complete remission with conventional chemotherapy. Pediatric Hematology and Oncology. 2003; 20(3):201-210.
Not applicable

Katzenstein HM, Rigsby C, Shaw PH, Mitchell TL, Haut PR, Kletzel M. Novel therapeutic approaches in the treatment of children with hepatoblastoma. Journal of Pediatric Hematology/Oncology. 2002;24(9):751-755.
Not applicable; specific details not reported

Kusnierczyk NMA, Saunders EF, Dupuis LL. Outcomes of antiemetic prophylaxis in children undergoing bone marrow transplantation. Bone Marrow Transplantation. 2002;30(2):119-124.
Not applicable

Renner S, Krumpelmann S, Bruchelt G, Wiesinger H, Niethammer D, Klingebiel T. Effect of amifostine on neuroblastoma during high dose chemotherapy: In vivo and in vitro investigations. Anticancer Research. 2000;20(6B):4531-4538.
Not applicable

Coppes MJ, Yanofsky R, Pritchard S, Leclerc J-M, Howard DR, Perrotta M, Keays S, Pyesmany A, Dempsey E, Pratt CB. Safety, tolerability, antiemetic efficacy, and pharmacokinetics of oral dolasetron mesylate in pediatric cancer patients receiving moderately to highly emetogenic chemotherapy. Journal of Pediatric Hematology/Oncology. 1999;21(4):274-283.
Not applicable; not extensively referenced

Diaz MA, Vicent MG, Madero L. High-dose busulfan/melphalan as conditioning for autologous PBPC transplantation in pediatric patients with solid tumors. Bone Marrow Transplantation. 1999;24(11):1157-1159.
Not applicable

Matsuyama T, Kojima S, Kato K. Allogeneic bone marrow transplantation for childhood leukemia following a busulfan and melphalan preparative regimen. Bone Marrow Transplantation. 1998;22(1):21-26.
Specific details not reported

Chan KW, Petropoulos D, Choroszy M, Herzog C, Jaffe N, Ater J, Korbling M. High-dose sequential chemotherapy and autologous stem cell reinfusion in advanced pediatric solid tumors. Bone Marrow Transplantation. 1997;20(12):1039-1043.
Not applicable

Adamson PC, Balls FM, Belasco JE, Lange B, Berg SL, Blaney SM, Graig C, Poplack DG. A phase I trial of amifostine (WR-2721) and melphalan in children with refractory cancer. Cancer Research. 1995;55(18):4069-4072.
Not applicable

Otten J, Hachimi-Idrissi S, Balduck N, Maurus R. Prevention of emesis by tropisetron (Navoban) in children receiving cytotoxic therapy for solid malignancies. Seminars in Oncology. 1994;21(5 Suppl.9):17-19.
Not applicable

McQueen KD, Milton JD. Multicenter postmarketing surveillance of ondansetron therapy in pediatric patients. Annals of Pharmacotherapy. 1994;28(1):85-92.
Not applicable

Matera MG, Di Tullio M, Lucarelli C, Casale F, Calabria C, Lampa E, Indolfi P, Rossi F. Ondansetron, an antagonist of 5-HT_3 receptors, in the treatment of antineoplastic drug-induced nausea and vomiting in children. Journal of Medicine. 1993;24(2-3):161-170.
Not applicable

Hachimi-Idrissi S, De Schepper J, Maurus R, Otten J. Prevention of emesis by ICS 205-930 in children receiving cytotoxic chemotherapy. European Journal of Cancer Part A: General Topics. 1993;29(6):854-856.
Not applicable

Ries F, Dicato MA. Emesis control in hematological-oncology. Leukemia and Lymphoma. 1992;7(Suppl.2):83-89.
Review article

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

Ovid MEDLINE(R) 1950 to September Week 2 2009

exp 6-Mercaptopurine/	15925
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)")	3899
exp Vomiting/	21430
3 and 2	13

Colli MV, Amaro TA, Pinto AL, Gaburri PD, Chebli JM. Azathioprine toxicity in Crohn's disease: incidence, approach and course. Revista Da Associacao Medica Brasileira. 2008;54(5):415-21.
Article not in English/French (Portuguese)

Sastry J, Karandikar SS, English MW. Benign intracranial hypertension in association with acute lymphoblastic leukemia. Pediatric Hematology & Oncology. 2003;20(2):157-60.
Not applicable

Avvisati G, Petti MC, Lo-Coco F, Vegna ML, Amadori S, Baccarani M, Cantore N, Di Bona E, Ferrara F, Fioritoni G, Gallo E, Invernizzi R, Lazzarino M, Liso V, Mariani G, Ricciuti F, Selleri C, Sica S, Veneri D, Mandelli F. GIMEMA (Gruppo Italiano Malattie Ematologische dell'Adulto) Italian Cooperative Group. Induction therapy with idarubicin alone significantly influences event-free survival duration in patients with newly diagnosed hypergranular acute promyelocytic leukemia: final results of the GIMEMA randomized study LAP 0389 with 7 years of minimal follow-up. Blood. 2001;100(9):3141-6.
Specific details not reported

Parker RI, Prakash D, Mahan RA, Giugliano DM, Atlas MP. Randomized, double-blind, crossover, placebo-controlled trial of intravenous ondansetron for the prevention of intrathecal chemotherapy-induced vomiting in children. Journal of Pediatric Hematology/Oncology. 2001;23(9):578-81.
Not applicable

Korelitz BI, Glass JL, Wisch N. Long-term immunosuppressive therapy of ulcerative colitis. Continuation of a personal series. American Journal of Digestive Diseases. 1973;18(4):317-22.
Not applicable

Aur RJ, Verzosa MS, Hustu HO, Simone JV. Response to combination therapy after relapse in childhood acute lymphocytic leukemia. Cancer. 1972;30(2):334-8.
Specific details not reported

Onuma T, Rosner F, Levy RN, Cuttner J, Moon JH, Silver RT, Blom J, Falkson G, Burningham R, Glidewell O, Holland JF. Treatment of adult leukemia with L-asparaginase (NSC-109229). Cancer Chemotherapy Reports - Part 1. 1971;55(3):269-75.
Adult data

Schafer KH, Blaker F. Experiences with immunosuppressive therapy in childhood ulcerative colitis. Zeitschrift fur Kinderheilkunde. 1971;110(4):317-23.
Not applicable

Kampfen P, Hodler J. Treatment of chronic glomerulonephritis with imuran.
Schweizerische Medizinische Wochenschrift. Journal Suisse de Medecine. 1970;100(49):2093-100.
Article not in English/French (German)

Cirla E, Guastalla A, Tosi S, Caruso I, Fantini F. [Effects of azathioprine in the treatment of rheumatoid arthritis]. Reumatismo. 1969;21(6):370-80.
Article not in English/French (Italian)

Sharpstone P, Ogg CS, Cameron JS. Nephrotic syndrome due to primary renal disease in adults: II. A controlled trial of prednisolone and azathioprine. British Medical Journal. 1969;2(5656):535-9.
Adult data

Theodor E, Gilon E, Waks U. Treatment of ulcerative colitis with azathioprine. British Medical Journal. 1968;4(5633):741-3.
Not applicable

Hyman CB, Bogle JM, Brubaker CA, Williams K, Hammond D. Central nervous system involvement by leukemia in children. I. Relationship to systemic leukemia and description of clinical and laboratory manifestation. Blood. 1965;25:1-12.
Not applicable

EMBASE

exp mercaptopurine/ae, to [Adverse Drug Reaction, Drug Toxicity]	1932
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>)	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

Peng X-S, Pan T, Chen L-Y, Huang G, Wang J. Langerhans' cell histiocytosis of the spine in children with soft tissue extension and chemotherapy. International Orthopaedics. 2009;33(3):731-736.
Specific details not reported

Bay A, Oner AF, Cesur Y, Dogan M, Etlik O, Sanli F. Symptomatic hypoglycemia: An unusual side effect of oral purine analogues for treatment of ALL. Pediatric Blood and Cancer. 2006;47(3):330-331.
Specific details not reported

Laver JH, Kraveka JM, Hutchison RE, Chang M, Kepner J, Schwenn M, Tarbell N, Desai S, Weitzman S, Weinstein HJ, Murphy SB. Advanced-stage large-cell lymphoma in children and adolescents: Results of a randomized trial incorporating intermediate-dose methotrexate and high-dose cytarabine in the maintenance phase of the APO regimen: A pediatric oncology group phase III trial. Journal of Clinical Oncology. 2005;23(3):541-547.
N**ot applicable; not specific to mercaptopurine**

Hyams J.S. Inflammatory bowel disease. Pediatrics in Review. 26(9)(pp 308-314), 2005.
Not applicable

Cappelli C, Ragni G, De Pasquale MD, Gonfiantini M, Russo D, Clerico A. Tropisetron: Optimal dosage for children in prevention of chemotherapy-induced vomiting. Pediatric Blood and Cancer. 2005;45(1):48-53.
Not applicable

Corapcioglu F, Sarper N. A prospective randomized trial of the antiemetic efficacy and cost-effectiveness of intravenous and orally disintegrating tablet of ondansetron in children with cancer. Pediatric Hematology and Oncology. 2005;22(2):103-114.
Specific details not reported

Sarnaik SA. Management of immunocompromized children with cancers - Role of the primary care physician. Indian Journal of Practical Pediatrics. 2003;5(1):25-28.
Not applicable

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Review article

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Specific details not reported

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Not applicable

Ziino O, Russo D, Orlando MA, Benigno V, Locatelli F, Arico M. Symptomatic hypoglycemia in children receiving oral purine analogues for treatment of childhood acute lymphoblastic leukemia. Medical and Pediatric Oncology. 2002;39(1):32-34.
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Specific details not reported

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Previously reviewed; specific details not reported

Halonen P, Salo MK, Makipernaa A. Fasting hypoglycemia is common during maintenance therapy for childhood acute lymphoblastic leukemia. Journal of Pediatrics. 2001;138(3):428-431.
Not applicable

Stockhorst U, Spennes-Saleh S, Korholz D, Gobel U, Schneider ME, Steingruber H-J, Klosterhalfen S. Anticipatory symptoms and anticipatory immune responses in pediatric cancer patients receiving chemotherapy: Features of a classically conditioned response?. Brain, Behavior, and Immunity. 2000;14(3):198-218.
Not applicable

Harris MB, Shuster JJ, Pullen J, Borowitz MJ, Carroll AJ, Behm FG, Camitta B, Land VJ. Treatment of children with early pre-B and pre-B acute lymphocytic leukemia with antimetabolite-based intensification regimens: A pediatric oncology group study. Leukemia. 2000;14(9):1570-1576.
Not applicable

Uysal KM, Olgun N, Sarialioglu F. Tropisetron in the prevention of chemotherapy - Induced acute emesis in pediatric patients. Turkish Journal of Pediatrics. 1999;41(2):207-218.
Not applicable

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Not applicable

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Specific details not reported

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Not applicable

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Previously reviewed; specific details not reported

Abrahamov A, Mechoulam R. An efficient new cannabinoid antiemetic in pediatric oncology. Life Sciences. 1995;56(23-24):2097-2102.
Not applicable

Benoit Y, Hulstaert F, Vermylen C, Sariban E, Hoyoux C, Uyttebroeck A, Otten J, Laureys G, De Kerpel I, Nortier D, Ritter L, De Keyser P. Control of nausea and vomiting by Navoban (tropisetron) in 131 children receiving cytotoxic chemotherapy. Anti-Cancer Drugs. 1995;6(Suppl. 1):9-14.
Specific details not reported

Cohen IJ, Zehavi N, Buchwald I, Yaniv Y, Goshen Y, Kaplinsky C, Zaizov R. Oral ondansetron: An effective ambulatory complement to intravenous ondansetron in the control of chemotherapy-induced nausea and vomiting in children. Pediatric Hematology and Oncology. 1995;12(1):67-72.
Specific details not reported

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Not applicable

Quah TC, Lam SK. Recent advances in childhood acute lymphoblastic leukemia. Journal of the Singapore Paediatric Society. 1992;34(1-2): 92-98.
Review article

McLeod HL, Relling MV, Crom WR, Silverstein K, Groom S, Rodman JH, Rivera GK, Crist WM, Evans WE. Disposition of antineoplastic agents in the very young child. British Journal of Cancer. 1992;66(Suppl. 18):S23-S29.
Not applicable

Deriu L, Nardelli S. Evolution of antiemetic treatment in hematologic patients. Leukemia and Lymphoma. 1992;7(Suppl. 2):78-82.
Review article

Giona F, Testi AM, Moleti ML, Annino L, Meloni G, Arcese W, Rolla M, Madon E, Specchia G, Rotoli B, Ladogana S, Zanesco L, Rondelli R, Pession A, Mandelli F. IdaRubicin plus Cytosine-Arabinoside (ALL R-87 protocol) in advanced acute lymphoblastic leukemia: The GIMEMA/AIEOP experience. Leukemia and Lymphoma. 1992;7(Suppl. 2):15-18.
Pediatric data grouped with adult data

Nakadate H, Hatayama Y, Hatae Y, Takeda T. BH-AC.AMP protocol in the treatment of refractory childhood acute leukemia. Japanese Journal of Cancer and Chemotherapy. 1988;15(10):2907-2910.
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

Chen J-X, Lu Y-C, Xu T, Sun K-H, Hu G-H, Luo C, Yu M-K, Wang C-L, Lu L-Q, Yan Y. Microsurgery and comprehensive treatment strategies for callosal gliomas. Academic Journal of Second Military Medical University. 2009;30(4):364-368.
Not applicable

Bernhard MK, Hugle B, Merkenschlager A. Elevated liver enzymes under therapy with methylphenidate in a boy with T-cell leukemia. Journal of Pediatric Neurology. 2009;7(3):297-299.
Not applicable

Stefanowicz J, Izycka-Swieszewska E, Drozynska E, Pienczk J, Polczynska K, Czauderna P, Sierota D, Bien E, Stachowicz-Stencel T, Kosiak W, Balcerska A. Neuroblastoma and opsoclonus-myoclonus-ataxia syndrome - Clinical and pathological characteristics. Folia Neuropathologica. 2008;46(3):176-185.
Not applicable

Grewal JS, Smith LB, Winegarden III JD, Krauss JC, Tworek JA, Schnitzer B. Highly aggressive ALK-positive anaplastic large cell lymphoma with a leukemic phase and multi-organ involvement: A report of three cases and a review of the literature. Annals of Hematology. 2007;86(7):499-508.
Not applicable

Eich HT, Muller R-P, Micke O, Kocher M, Berthold F, Hero B. Esthesioneuroblastoma in childhood and adolescence: Better prognosis with multimodal treatment?. Strahlentherapie und Onkologie. 2005;181(6):378-384.
Not applicable

Pietila S, Ala-Houhala M, Lenko HL, Harmoinen APT, Turjanmaa V, Makipernaa A. Renal impairment and hypertension in brain tumor patients treated in childhood are mainly associated with cisplatin treatment. Pediatric Blood and Cancer. 2005;44(4):363-369.
Not applicable

Groninger E, Proost JH, De Graaf SSN. Pharmacokinetic studies in children with cancer. Critical Reviews in Oncology/Hematology. 2004;52(3):173-197.
Specific details not reported

Johnson TN. The development of drug metabolising enzymes and their influence on the susceptibility to adverse drug reactions in children. Toxicology. 2003;192(1):37-48.
Not applicable

Sandri A, Sardi N, Besenzon L, Cordero Di Montezemolo L, Ricardi U, Papalia F, Madon E. Brain stem tumors in pediatric age. Italian Journal of Pediatrics. 2002;28(1): 33-40.
Not applicable

De Rosa L, Lalle M, Pandolfi A, Ruscio C, Amodeo R. Autologous bone marrow transplantation with negative immunomagnetic purging for aggressive B-cell non-Hodgkin's lymphoma in first complete remission. Annals of Hematology. 2002;81(10): 575-581.
Not applicable

Aksoylar S, Akman SA, Ozgenc F, Kansoy S. Comparison of tropisetron and granisetron in the control of nausea and vomiting in children receiving combined cancer chemotherapy. Pediatric Hematology and Oncology. 2001;18(6):397-406.
Specific details not reported

Stockhorst U, Spennes-Saleh S, Korholz D, Gobel U, Schneider ME, Steingruber H-J, Klosterhalfen S. Anticipatory symptoms and anticipatory immune responses in pediatric cancer patients receiving chemotherapy: Features of a classically conditioned response?. Brain, Behavior, and Immunity. 2000;14(3):198-218.
Not applicable

Jing H, Ziping W, Liqiang Z. A randomized trial of Zudan in the prophylaxis of nausea and vomiting induced by cisplatin. Chinese Journal of Oncology. 1998;20(2):153-154.
Adult data

Salgado FGT, Ulloa FB, Loria A, Nieto M, Mateos CR. Flunitrazepam and dexamethasone to prevent the early onset of nausea and vomiting by cytotoxic chemotherapy. Revista del Instituto Nacional de Cancerologia. 1997;43(2):86-90.
Article not in English/French (Spanish)

Tyc VL, Mulhern RK, Jayawardene D, Fairclough D. Chemotherapy-induced nausea and emesis in pediatric cancer patients: An analysis of coping strategies. Journal of Pain and Symptom Management. 1995;10(5):338-347.
Not applicable

Benoit Y, Hulstaert F, Vermylen C, Sariban E, Hoyoux C, Uyttebroeck A, Otten J, Laureys G, De Kerpel I, Nortier D, Ritter L, De Keyser P. Control of nausea and vomiting by Navoban (tropisetron) in 131 children receiving cytotoxic chemotherapy. Anti-Cancer Drugs. 1995;6(Suppl.1):9-14.
Specific details not reported

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Not specific to teniposide

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Specific details not reported

Marina NM, Shema SJ, Bowman LC, Rodman J, Douglass EC, Furman WL, Pappo A, Santana VM, Hudson M, Meyer WH, Pratt CB. Failure of granulocyte-macrophage colony-stimulating factor to reduce febrile neutropenia in children with recurrent solid tumors treated with ifosfamide, carboplatin, and etoposide chemotherapy. Medical and Pediatric Oncology. 1994;23(4):328-334.
Specific details not reported

Jacobson SJ, Shore RW, Greenberg M, Spielberg SP. The efficacy and safety of granisetron in pediatric cancer patients who had failed standard antiemetic therapy during anticancer chemotherapy. American Journal of Pediatric Hematology/Oncology. 1994;16(3):231-235).
Specific details not reported

Sakata N, Okamura J, Eguchi H, Ikuno Y, Tasaka H. Meningeal neuroblastoma after completing therapy. Pediatric Hematology and Oncology. 1993;10(2):201-204.
Not applicable

Hachimi-Idrissi S, De Schepper J, Maurus R, Otten J. Prevention of emesis by ICS 205-930 in children receiving cytotoxic chemotherapy. European Journal of Cancer Part A: General Topics. 1993;29(6):854-856.
Not applicable

Quah TC, Lam SK. Recent advances in childhood acute lymphoblastic leukemia. Journal of the Singapore Paediatric Society. 1992;34(1-2):92-98.
Review article

McLeod HL, Relling MV, Crom WR, Silverstein K, Groom S, Rodman JH, Rivera GK, Crist WM, Evans WE. Disposition of antineoplastic agents in the very young child. British Journal of Cancer. 1992;66(Suppl.18):S23-S29.
Not applicable

Ries F, Dicato MA. Emesis control in hematological-oncology. Leukemia and Lymphoma. 1992;7(Suppl.2):83-89.
Review article; not applicable

Bassan R, Cornelli PE, Battista R, Terzi F, Buelli M, Rambaldi A, Viero P, D'Emilio A, Dini E, Barbui T. Intensive retreatment of adults and children with acute lymphoblastic leukemia. Hematological Oncology. 1992;10(2):105-110.
Specific details not reported

Hadjilaskari P, Henze G. Gastrointestinal non-Hodgkin's lymphomas in childhood. Verdauungskrankheiten. 1989;7(2):41-47.
Article not in English (German)

Chan HSL, Correia JA, MacLeod SM. Nabilone versus prochlorperazine for control of cancer chemotherapy-induced emesis in children: A double-blind, crossover trial. Pediatrics. 1987;79(6):946-952.
Data not specific to teniposide

Sanz GF, Sanz MA, Rafecass FJ. Teniposide and cytarabine combination chemotherapy in the treatment of relapsed adolescent and adult acute lymphoblastic leukemia. Cancer Treatment Reports. 1986;70(11):1321-1323.
Adolescent and adult data

Ratcliffe JM, Nobbs J, Campbell RWF. Continuous ECG monitoring of children with cancer receiving domperidone. Pediatric Hematology and Oncology. 1986;3(4):343-346.
Specific details not reported

Dalzell AM, Bartlett H, Lilleyman JS. Nabilone: An alternative antiemetic for cancer chemotherapy. Archives of Disease in Childhood. 1986;61(5):502-505.
Not applicable

Pastore G, De Bernardi B, Carli M. Peptichemio in neuroblastoma at relapse. Medical and Pediatric Oncology. 1984;12(3):162-165.
The three patients reported to have experienced nausea/vomiting did not receive teniposide

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Adolescent data

Rivera G, Bowman WP, Murphy SB. VM-26 with prednisone and vincristine for treatment of refractory acute lymphocytic leukemia. Medical and Pediatric Oncology. 1982;10(5):439-446.
Not applicable

Smith SD. Advances in the pharmacology of cancer chemotherapy. Pediatric Clinics of North America. 1981;28(1):145-160.
Review article

Rosenstock JG, Donaldson MH. Phase I-II trial of VM 26 (NSC 122819) in the treatment of children with late stage leukemia. Cancer Treat Rep. 1976;60(3):265-267.
Specific details not reported

Rodman JH, Abromowitch M, Sinkule JA, Hayes FA, Rivera GK, Evans WE. Clinical pharmacodynamics of continuous infusion teniposide: systemic exposure as a determinant of response in a phase I trial. J Clin Oncol 1987;5(7):1007–14.
Not applicable

Evans WE, Rodman JH, Relling MV, et al. Differences in teniposide disposition and pharmacodynamics in patients with newly diagnosed and relapsed acute lymphocytic leukemia. J Pharmacol Exp Ther 1992;260(1):71–7.
Not applicable

Sinkule JA, Stewart CF, Crom WR, Melton ET, Dahl GV, Evans WE. Teniposide (VM26) disposition in children with leukemia. Cancer Res 1984;44(3):1235–7.
Not applicable

12. LITERATURE SEARCH: VINDESINE-INDUCED NAUSEA AND VOMITING IN CHILDREN

Ovid MEDLINE(R) 1950 to Present with Daily Update

exp Vindesine/	1200
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)")	129
exp Vomiting/	21230
3 and 2	2

Lorent N, De Leyn P, Lievens Y, Verbeken E, Nackaerts K, Dooms C, Van Raemdonck D, Anrys B, Vansteenkiste J. Leuven Lung Cancer Group. Long-term survival of surgically staged IIIA-N2 non-small-cell lung cancer treated with surgical combined modality approach: analysis of a 7-year prospective experience. Annals of Oncology. 2004;15(11):1645-53.

Adult data

Jungnelius U, Ringborg U, Aamdal S, Mattsson J, Stierner U, Ingvar C, Malmstrom P, Andersson R, Karlsson M, Willman K, Wist E, Bjelkengren G, Westberg R. acarbazine-vindesine versus dacarbazine-vindesine-cisplatin in disseminated malignant melanoma. A randomised phase III trial. European Journal of Cancer. 1998;34(9):1368-74.

Adolescent and adult data

EMBASE 1980 to 2009 Week 31

exp vindesine/	5883
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>)	330
exp "nausea and vomiting"/ or exp vomiting/	122213
3 and 2	33

Xue S-L, Wu D-P, Sun A-N, Tang X-W. CAG regimen enables relapsed or refractory T-cell acute lymphocytic leukemia patients to achieve complete remission: A report of six cases. American Journal of Hematology. 2008;83(2):167-170.

Adult data

Aleman BMP, Raemaekers JMM, Tomisic R, Baaijens MHA, Bortolus R, Lybeert MLM, van der Maazen RWM, Girinsky T, Demeestere G, Lugtenburg P, Lievens Y, de Jong D, Pinna A, Henry-Amar M. Involved-field radiotherapy for patients in partial remission after chemotherapy for advanced Hodgkin's lymphoma. International Journal of Radiation Oncology Biology Physics. 2007;67(1):19-30.

Adolescent and adult data

Arima F, Sueoka E, Mukai K, Tajima K, Fukuda H, Mikuni C, Alkawa K, Kasai M, Kiyama Y, Miura I, Miura A, Sai T, Sasaki Y, Itoh K, Shimoyama M, Tobinai K, Minato K, Takenaka T, Takeyama K, Kohno A, Sawada U, Aoki I, Kawano K, Ibuka T, Miwa T, Togawa A, Yamada H, Iwase S, Deura K, Seki S, Ogura M, Kagami Y, Suzuki H, Nagai H, Hotta T, Kinoshita T, Hirano M, Okamoto M, Shirakawa S, Kobayashi T, Masuya M, Yamaguchi M, Konda S, Masaki Y, Susuki T, Fukuhara S, Ohno H, Abe T, Taniwaki M, Ohno Y, Irino S, Nagai M, Uike N, Okamoto S, Fujita K, Izumi Y, Shimamoto Y, Fukushima H, Yamaguchi K, Takatsuki K, Matsumoto M, Hanada S, Uozumi K, Utsunomiya A, Araki K, Ohshiro I. Phase II study of chemotherapy and stem cell transplantation for adult acute lymphoblastic leukemia or lymphoblastic lymphoma: Japan Clinical Oncology Group study 9004. Cancer Science. 2007;98(9):1350-1357.

Adolescent and adult data

De Labarthe A, Rousselot P, Huguet-Rigal F, Delabesse E, Witz F, Maury S, Rea D, Cayuela J-M, Vekemans M-C, Reman O, Buzyn A, Pigneux A, Escoffre M, Chalandon Y, MacIntyre E, Lheritier V, Vernant J-P, Thomas X, Ifrah N, Dombret H. Imatinib combined with induction or consolidation chemotherapy in patients with de novo Philadelphia chromosome-positive acute lymphoblastic leukemia: Results of the GRAAPH-2003 study. Blood. 2007;109(4):1408-1413.
Adolescent and adult data

Gandemer V, Deley M-CL, Dollfus C, Auvrignon A, Bonnaure-Mallet M, Duval M, Lumley LD, Hartmann O, Mechinaud F, Sirvent N, Orbach D, Doireau V, Boutard P, Dalle J-H, Reguerre Y, Pautard B, Aubier F, Schneider P, Suc A, Couillaut G, Schmitt C. Multicenter randomized trial of chewing gum for preventing oral mucositis in children receiving chemotherapy. Journal of Pediatric Hematology/Oncology. 2007;29(2):86-94.
Not applicable

Grewal JS, Smith LB, Winegarden III JD, Krauss JC, Tworek JA, Schnitzer B. Highly aggressive ALK-positive anaplastic large cell lymphoma with a leukemic phase and multi-organ involvement: A report of three cases and a review of the literature. Annals of Hematology. 2007;86(7):499-508.
Not applicable

Meier C, Kapellen T, Trobs RB, Hirsch W, Parwaresch R, Kiess W, Korholz D. Temporary diabetes mellitus secondary to a primary pancreatic Burkitt lymphoma. Pediatric Blood and Cancer. 2006;47(1):94-96.
Not applicable

Gobbi PG, Broglia C, Levis A, La Sala A, Valentino F, Chisesi T, Sacchi S, Corbella F, Cavanna L, Iannitto E, Pavone V, Molica S, Corazza GR, Federico M. MOPPEBVCAD chemotherapy with limited and conditioned radiotherapy in advanced Hodgkin's lymphoma: 10-Year results, late toxicity, and second tumors. Clinical Cancer Research. 2006;12(2):529-535.
Adult data

Gobbi PG, Levis A, Chisesi T, Broglia C, Vitolo U, Stelitano C, Pavone V, Cavanna L, Santini G, Merli F, Liberati M, Baldini L, Deliliers GL, Angelucci E, Bordonaro R, Federico M. ABVD versus modified Stanford V versus MOPPEBVCAD with optional and limited radiotherapy in intermediate- and advanced-stage Hodgkin's lymphoma: Final results of a multicenter randomized trial by the Intergruppo Italiano Linfomi.
Journal of Clinical Oncology. 2005;23(36):9198-9207.
Adult data

Miyawaki S, Sakamaki H, Ohtake S, Emi N, Yagasaki F, Mitani K, Matsuda S, Kishimoto Y, Miyazaki Y, Asou N, Matsushima T, Takahashi M, Ogawa Y, Honda S, Ohno R. A randomized, postremission comparison of four courses of standard-dose consolidation therapy without maintenance therapy versus three courses of standard-dose consolidation with maintenance therapy in adults with acute myeloid leukemia: The Japan Adult Leukemia Study Group AML97 study. Cancer. 2005;104(12):2726-2734.
Adolescent and adult data

Shiozawa Y, Kiyokawa N, Fujimura J, Suzuki K, Yarita Y, Fujimoto J, Saito M, Yamashiro Y. Primary malignant lymphoma of the central nervous system in an immunocompetent child: A case report. Journal of Pediatric Hematology/Oncology. 2005;27(10):561-564.
Not applicable

Nakagawa H, Miyahara E, Suzuki T, Wada K, Tamura M, Fukushima Y.
Continuous intrathecal administration of 5-fluoro-2'-deoxyuridine for the treatment of neoplastic meningitis. Neurosurgery. 2005;57(2):266-279.
Not applicable

Eich HT, Muller R-P, Micke O, Kocher M, Berthold F, Hero B. Esthesioneuroblastoma in childhood and adolescence: Better prognosis with multimodal treatment?
Strahlentherapie und Onkologie. 2005;181(6):378-384.
Not applicable

Milpied N, Deconinck E, Gaillard F, Delwail V, Foussard C, Berthou C, Gressin R, Lucas V, Colombat P, Harousseau J-L. Initial Treatment of Aggressive Lymphoma with High-Dose Chemotherapy and Autologous Stem-Cell Support. New England Journal of Medicine. 2004;350(13):1287-1295.
Adolescent and adult data

Kremens B, Wieland R, Reinhard H, Neubert D, Beck JD, Klingebiel T, Bornfeld N, Havers W. High-dose chemotherapy with autologous stem cell rescue in children with retinoblastoma. Bone Marrow Transplantation. 2003;31(4):281-284.
Not applicable

Langebrake C, Reinhardt D, Ritter J. Minimising the long-term adverse effects of childhood leukaemia therapy. Drug Safety. 2002;25(15):1057-1077.
Review article; not applicable

Zeng XY, Wang AH, Liu YF, Chen Y, Shen Y, Shen ZX. Ramosetron for the management of chemotherapy-induced gastrointestinal events in patients with hematological malignancies. Methods and Findings in Experimental and Clinical Pharmacology. 2001;23(4):191-195.
Adult data

Martino R, Bellido M, Brunet S, Altes A, Sureda A, Guardia R, Aventin A, Nomdedeu JF, Domingo-Albos A, Sierra J. Intensive salvage chemotherapy for primary refractory or first relapsed adult acute lymphoblastic leukemia: Results of a prospective trial. Haematologica. 1999;84(6):505-510.
Adolescent and adult data

Giona F, Annino L, Testi AM, Rondelli R, Arcese W, Meloni G, Moleti ML, Mandelli F.
Management of advanced acute lymphoblastic leukemia in children and adults: Results of the ALL R-87 protocol. Leukemia and Lymphoma. 1998;32(1-2):89-95.
Not applicable

Tanimoto M, Miyawaki S, Ino T, Kyo T, Sakamaki H, Naoe T, Hiraoka A, Asou N, Ohshima T, Tsubaki K, Kuriyama K, Ueda T, Minamil S, Okabe K-I, Saito H, Murakami H, Hirano M, Dohy H, Onozawa Y, Suzuki H, Ohno R. Response-oriented individualized induction therapy followed by intensive consolidation and maintenance for adult patients with acute lymphoblastic leukemia: The ALL-87 study of the Japan Adult Leukemia Study Group (JALSG). International Journal of Hematology. 1998;68(4):421-429.
Adolescent and adult data

Jungnelius U, Ringborg U, Aamdal S, Mattsson J, Stierner U, Ingvar C, Malmstrom P, Andersson R, Karlsson M, Willman K, Wist E, Bjelkengren G, Westberg R. Dacarbazine-vindesine versus dacarbazine-vindesine-cisplatin in disseminated malignant melanoma. A randomised phase III trial. European Journal of Cancer. 1998;34(9):1368-1374.
Adolescent and adult data

Gobbi PG, Pieresca C, Ghirardelli ML, Di Renzo N, Federico M, Merli F, Iannitto E, Pitini V, Grignani G, Donelli A, Carotenuto M, Silingardi V, Ascari E. Long-term results from MOPPEBVCAD chemotherapy with optional limited radiotherapy in advanced Hodgkin's disease. Blood. 1998;91(8):2704-2712.
Adolescent and adult data

Ginopoulos P, Spyropoulos K, Kardamakis D, Dougenis D, Onyenadum A, Gogos CH, Solomou E, Chrysanthopoulos K. Advanced non-small cell lung cancer chemotherapy: A randomized trial of two active regimens (MVP and PE). Cancer Letters. 1997;119(2):241-247.
Adult data; not applicable

Abrahamov A, Mechoulam R. An efficient new cannabinoid antiemetic in pediatric oncology. Life Sciences. 1995;56(23-24):2097-2102.
Not specific to vindesine

Benoit Y, Hulstaert F, Vermylen C, Sariban E, Hoyoux C, Uyttebroeck A, Otten J, Laureys G, De Kerpel I, Nortier D, Ritter L, De Keyser P. Control of nausea and vomiting by Navoban (tropisetron) in 131 children receiving cytotoxic chemotherapy. Anti-Cancer Drugs. 1995;6(Suppl.1):9-14.
Previously reviewed; not applicable

Otten J, Hachimi-Idrissi S, Balduck N, Maurus R. Prevention of emesis by tropisetron (Navoban) in children receiving cytotoxic therapy for solid malignancies. Seminars in Oncology. 1994;21(5Suppl.9):17-19.
Not specific to vindesine

Mulder NH, Van der Graaf WTA, Willemse PHB, Schraffordt Koops H, De Vries EGE, Sleijfer TD. Dacarbazine (DTIC)-based chemotherapy or chemoimmunotherapy of patients with disseminated malignant melanoma. British Journal of Cancer. 1994;70(4):681-683.
Adult data

Furuse K, Nishi T, Hirose Y, Sumisaka O, Kikkawa M. Prevention and treatment of adverse effects from chemotherapy for bone and soft tissue sarcomas. IRYO - Japanese Journal of National Medical Services. 1994;48(8):598-605.
Article not in English/French

Jackson GH, Lennard AL, Taylor PRA, Carey P, Angus B, Lucraft H, Evans RGB, Proctor SJ, Abela M, Bradford C, Browning N, Cartner R, Chandler J, Condie P, Dewar M, Finney R, Galloway M, Goff D, Hendrick A. Autologous bone marrow transplantation in poor-risk high-grade non-Hodgkin's lymphoma in first complete remission. British Journal of Cancer. 1994;70(3):501-505.
Adult data

Martino R, Brunet S, Sureda A, Mateu R, Altes A, Domingo-Albos A.
Treatment of refractory and relapsed adult acute leukemia using a uniform chemotherapy protocol. Leukemia and Lymphoma. 1993;11(5-6):393-398.
Adult data

Bleiberg H, Van Belle S, Paridaens R, De Wasch G, Dirix LY, Tjean M.
Compassionate use of tropisetron in patients at high risk of severe emesis.
Annals of Oncology. 1993;4(Suppl.3):S43-S45.
Specific details not reported

Giona F, Testi AM, Moleti ML, Annino L, Meloni G, Arcese W, Rolla M, Madon E, Specchia G, Rotoli B, Ladogana S, Zanesco L, Rondelli R, Pession A, Mandelli F.
IdaRubicin plus Cytosine-Arabinoside (ALL R-87 protocol) in advanced acute lymphoblastic leukemia: The GIMEMA/AIEOP experience. Leukemia and Lymphoma. 1992;7(Suppl. 2):15-18.
Specific details not reported

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

Ovid MEDLINE(R) 1950 to September Week 2 2009

exp Asparaginase/	3393
exp Polyethylene Glycols/	33454
1 and 2	136
limit 3 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)")	63
exp Vomiting/	21595
4 and 5	0

EMBASE 1980 to 2009 Week 43

exp asparaginase macrogol/	267
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>)	80
exp "nausea and vomiting"/ or exp vomiting/	125292
3 and 2	7

Soyer OU, Aytac S, Tuncer A, Cetin M, Yetgin S, Sekerel BE. Alternative algorithm for L-asparaginase allergy in children with acute lymphoblastic leukemia. Journal of Allergy and Clinical Immunology. 2009;123(4):895-899.
Not applicable

Douer D, Yampolsky H, Cohen LJ, Watkins K, Levine AM, Periclou AP, Avramis VI. Pharmacodynamics and safety of intravenous pegaspargase during remission induction in adults aged 55 years or younger with newly diagnosed acute lymphoblastic leukemia. Blood. 2007;109(7):2744-2750.
Adolescent and adult data

Langebrake C, Reinhardt D, Ritter J. Minimising the long-term adverse effects of childhood leukaemia therapy. Drug Safety. 2002;25(15):1057-1077.
Not applicable; review

Alvarez OA, Zimmerman G. Pegaspargase-induced pancreatitis. Medical and Pediatric Oncology. 2000;34(3):200-205.
Not applicable

Arnaout MK, Tamburro RF, Bodner SM, Sandlund JT, Rivera GK, Pui CH, Ribeiro RC.
Bacillus cereus causing fulminant sepsis and hemolysis in two patients with acute leukemia. Journal of Pediatric Hematology/Oncology. 1999;21(5):431-435.
Not applicable

Pento JT. Pegaspargase. Antineoplastic. Drugs of the Future. 1994;19(9):838-840.
Review article

Keating MJ, Holmes R, Lerner S, Hsi Ho D. L-asparaginase and PEG asparaginase - Past, present, and future. Leukemia and Lymphoma. 1993;10(Suppl):153-157.
Review article

APPENDIX B: WEBSITES SEARCHED FOR GUIDELINES AND STANDARDS

WEBSITES SEARCHED

CANADIAN CANCER ACADEMIC CENTERS

Alberta Cancer Board: www.cancerboard.ab.ca
British Columbia Cancer Agency: www.bc.cancer.ca
Cancer Care Nova Scotia: http://www.cancercare.ns.ca/site-cc/media/cancercare/NauseaVomitingFullVersion.pdf
Cancer Care Ontario Practice Guideline Initiative
Saskatchewan Cancer Agency: 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
International Oncology Network
Monroe Carell Jr's Children's Hospital of Vanderbilt: www.vanderbiltchildrens.com
National Cancer Institute:
http://www.cancer.gov/cancertopics/pdq/supportivecare/nausea/HealthProfessional/page1
St. Jude's Children's: www.stjude.org*

PROFESSIONAL ASSOCIATIONS AND AGENCIES

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

ACADEMIC AND GOVERNMENT ASSOCIATED WEBSITES

NCI: {HYPERLINK "http://www.nci.nih.gov/cancertopics"}
New Zealand Guidelines Group: www.qualityhealth.org.nz
SIGN: www.sign.ac.uk
National Institute for Health and Clinical Excellence: www.nice.org.ul (guidance.nice.org.uk)

CANCER RESOURCE WEBSITES

Cancer Backup (UK)
Cancer Index: www.cancerindex.org
National Comprehensive Cancer Network (NCCN)

GUIDELINE SPECIFIC WEBSITES

Cochrane Collaboration
National Guidelines Clearinghouse (NGC): www.guideline.gov
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

GUIDELINE: HESKETH PJ, KRIS MG, GRUNBERG SM, BECK T, HAINSWORTH JD, HARKER G, AAPRO MS, GANDARA D, LINDLEY CM. PROPOSAL FOR CLASSIFYING THE ACUTE EMETOGENICITY OF CANCER CHEMOTHERAPY. JOURNAL OF CLINICAL ONCOLOGY 1997;15:103-109

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	1	9	1	1	1	3		2	2
Rater#2	4	4	4	12	2	1	4	2	9	4	3	3	3	3	1	2	19	3		4	4	11	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	3	2	1	3
Rater#6	4	4	4	12	1	1	4	1	7	2	2	3	1	3	1	1	13	4	2	4	4	14	1	1	1	3	3	1	4
Rater#7	4	4	2	10	1	1	1	1	4	2	1	3	1	3	1	1	12	4	1	3	2	10	1	1	1	3		1	1
Obtained Score				55					33								80					56				15			13
Minimal Score				15					20								35					20				15			10
Maximum Score				60					80								140					80				60			40
Obtained-Minimal				40					13								45					36				0			3
Maximum-Minimal				45					60								105					60				45			30
Standardized Domain Scores				89					22								43					60				0			10

GUIDELINE: KRIS MG, HESKETH PJ, SOMERFIELD MR, ET AL. AMERICAN SOCIETY OF CLINICAL ONCOLOGY GUIDELINES FOR ANTIEMETICS IN ONCOLOGY: UPDATE 2006. JOURNAL OF CLINICAL ONCOLOGY 2006;24:2932-47

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	2	3	4	1	19	4		4	2	10	1	1	1	3		1	1
Rater#2	4	4	2	10	3	1	1	1	6	4	3	2	2	2	4	4	21	3		4	4	11	2	1	3	6		4	4
Rater#6	4	4	4	12	4	1	4	1	10	4	4	4	3	4	4	4	27	4	4	4	4	16	2	2	3	7	4	4	8
Rater#7	4	2	2	8	2	1	2	1	6	4	4	4	3	3	3	1	22	4	4	3	1	12	1	2	1	4		4	4
Obtained Score				40					28								89					49				20			17
Minimal Score				12					16								28					16				12			8
Maximum Score				48					64								112					64				48			32
Obtained-Minimal				28					12								61					33				8			9
Maximum-Minimal				36					48								84					48				36			24
Standardized Domain Scores				78					25								73					69				22			38

GUIDELINE: ANTIEMETIC TREATMENT GUIDELINES. MULTINATIONAL ASSOCIATION OF SUPPORTIVE CARE IN CANCER, 2008. (ACCESSED NOVEMBER 2008, 2008, AT HTTP://DATA.MEMBERCLICKS.COM/SITE/MASCC/MASCC_GUIDELINES_UPDATE.PDF)

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	2	1	9	4	3	2	1	3	3	4	20	3	1	4	4	12	1	1	2	4	1	1	2
Rater#3	3	3	2	8	3	1	3	2	9	2	3	3	3	2	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	4	11	4	1	3	3	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	8	3	2	3	2	3	2	4	19	3	3	2	2	10	1	3	3	7		1	1
Obtained Score				41					42								94					55				29			10
Minimal Score				15					20								35					20				15			10
Maximum Score				60					80								140					80				60			40
Obtained-Minimal				26					22								59					35				14			0
Maximum-Minimal				45					60								105					60				45			30
Standardized Domain Scores				58					37								56					58				31			0

GUIDELINE: SUPPORTIVE CARE GUIDELINES. CHILDREN'S ONCOLOGY GROUP. (ACCESSED OCTOBER 13, 2008, AT HTTPS://MEMBERS.CHILDRENSONCOLOGYGROUP.ORG/PROT/REFERENCE_MATERIALS.ASP)

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	1	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
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	3	1	4
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
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					28								38					28				15			10
Minimal Score				15					20								35					20				15			10
Maximum Score				60					80								140					80				60			40
Obtained-Minimal				18					8								3					8				0			0
Maximum-Minimal				45					60								105					60				45			30
Standardized Domain Scores				40					13								3					13				0			0

GUIDELINE: DUPUIS LL, MALONEY AM, NATHAN PC, NAQVI A, TABORI U. ANTIEMETIC SELECTION FOR CHILDREN RECEIVING ANTINEOPLASTICS AND/OR RADIOTHERAPY. IN: LAU E, ED. 2008-2009 DRUG HANDBOOK AND FORMULARY. TORONTO: SICKKIDS; 2008:246-51

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	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	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	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	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	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	7	4	1	3	3	11	1	1	1	3		1	1
Obtained Score				59					34								57					70				21			12
Minimal Score				18					24								42					24				18			12
Maximum Score				72					96								168					96				72			48
Obtained-Minimal				41					10								15					46				3			0
Maximum-Minimal				54					72								126					72				54			36
Standardized Domain Scores				76					14								12					64				6			0

GUIDELINE: ANTIEMESIS V.3.2009. NATIONAL COMPREHENSIVE CANCER NETWORK, 2009. (ACCESSED JULY 2, 2009, AT HTTP://WWW.NCCN.ORG/PROFESSIONALS/PHYSICIAN_GLS/PDF/ANTIEMESIS.PDF)

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	2	10	1	1	1	3		4	4
Rater#2	3	3	2	8	4	1	3	1	9	1	1	1	3	1	1	1	9	4		3	1	8	1	1	1	3	1	4	5
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	1	3
Rater#4	3	3	3	9	4	1	2	1	8	3	1	1	1	2	1	1	10	3	3	3	1	10	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	1	3
Obtained Score				44					44								65					56				20			19
Minimal Score				15					20								35					20				15			10
Maximum Score				60					80								140					80				60			40
Obtained-Minimal				29					24								30					36				5			9
Maximum-Minimal				45					60								105					60				45			30
Standardized Domain Scores				64					40								29					60				11			30

APPENDIX D: CATEGORIES AND GRADES OF EVIDENCE

NCCN CATEGORIES OF EVIDENCE AND CONSENSUS[10]

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[38]

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[39]

Grade of Recommendation	Benefit vs Risk and Burdens	Methodology	Implications
1A Strong recommendation, high-quality evidence	Desirable effects clearly outweigh undesirable effects or *vice versa*	Evidence from well done RCTs or Exceptional observational studies	Apply to most patients in most circumstances Further research unlikely to change recommendation
1B Strong recommendation, moderate quality evidence	Desirable effects clearly outweigh undesirable effects or *vice versa*	Evidence from RCTs with some flaws in study or Very strong evidence from observational studies	Apply to most patients in most circumstances Further research might be helpful
1C Strong recommendation, poor quality evidence	Desirable effects clearly outweigh undesirable effects or *vice versa*	Evidence of at least one critical outcome from observational studies, case series or RCTs with flaws	Apply to most patients in many circumstances Further research would be helpful
2A Weak recommendation, high quality evidence	Desirable effects closely balanced with undesirable effects	Consistent evidence from RCTs without important flaws or Exceptionally strong evidence from observational studies	Best action may depend on circumstances or patient or society values Further research unlikely to change recommendation
2B Weak recommendation, moderate quality evidence	Desirable effects closely balanced with undesirable effects	Evidence from RCTs with important flaws or Very strong evidence from observational studies	Best action dependent on patient circumstances or patient or society values Further research may change recommendation
2C Weak recommendation with poor quality evidence	Desirable effects closely balanced with undesirable effects	Evidence of at least one critical outcome from observational studies, case series or RCTs with serious flaws	Other alternatives may be equally reasonable Further research very likely to change recommendation

APPENDIX E: ALPHABETICAL LIST OF ANTINEOPLASTIC AGENT AND EMETIC RISK

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

Antineoplastic Agent	Level of Emetic Risk
5-Fluorouracil	Low
Aldesleukin > 12 to 15 million units/m^2	Moderate
Alemtuzumab	Minimal
Alpha interferon	Minimal
Altretamine	High
Amifostine > 300 mg/m^2	Moderate
Amifostine ≤ 300 mg/m^2	Low
Amsacrine	Low
Anthracycline + cyclophosphamide *Cyclophosphamide + doxorubicin *Cyclophosphamide + epirubicin	High
Arsenic trioxide	Moderate
Asparaginase (IM or IV)	Minimal
Azacitidine	Moderate
Bendamustine	Moderate
Bevacizumab	Minimal
Bexarotene	Low
Bleomycin	Minimal
Bortezomib	Minimal
Busulfan	Moderate
Busulfan (oral)	Low
Capecitabine	Low
Carboplatin*	High
Carmustine > 250 mg/m^2	High
Carmustine ≤ 250 mg/m^2 *	Moderate
Cetuximab	Minimal
Chlorambucil (oral)	Minimal
Cisplatin*	High
Cladribine (2-chlorodeoxyadenosine)	Minimal
Clofarabine*	Moderate
Cyclophosphamide (oral)	Moderate
Cyclophosphamide < 1 g/m^{2*}	Moderate
Cyclophosphamide ≥1 g/m^{2*}	High
Cyclophosphamide + anthracycline *Cyclophosphamide + doxorubicin *Cyclophosphamide + epirubicin	High
Cyclophosphamide + etoposide	High
Cytarabine > 200 mg to < 3 g/m^2	Moderate
Cytarabine ≤ 200 mg/m^2	Low
Cytarabine 3 g/m^2/dose*	High
Cytarabine 150-200 mg/m^2 + daunorubicin*	High

Antineoplastic Agent	Level of Emetic Risk
Cytarabine 300 mg/m^2 + etoposide*	High
Cytarabine 300 mg/m^2 + teniposide*	High
Cytarabine, methotrexate + hydrocortisone: Intrathecal therapy*	Moderate
Dacarbazine	High
Dactinomycin*	High
Daunorubicin*	Moderate
Daunorubicin + cytarabine 150-200 mg/m^2 *	High
Dasatinib	Minimal
Decitabine	Minimal
Denileukin diftitox	Minimal
Dexrazoxane	Minimal
Docetaxel	Low
Doxorubicin (liposomal)	Low
Doxorubicin*	Moderate
Doxorubicin + cyclophosphamide*	High
Doxorubicin + ifosfamide*	High
Doxorubicin + methotrexate 5 g/m^2	High
Epirubicin	Moderate
Epirubicin + cyclophosphamide*	High
Erlotinib	Minimal
Etoposide	Low
Etoposide (oral)	Moderate
Etoposide + cyclophosphamide*	High
Etoposide + cytarabine 300 mg/m^2 *	High
Etoposide + ifosfamide*	High
Fludarabine	Minimal
Fludarabine (oral)	Low
Gefitinib	Minimal
Gemcitabine	Low
Gemtuzumab ozogamicin	Minimal
Hydrocortisone, cytarabine + methotrexate: Intrathecal therapy*	Moderate
Hydroxyurea (oral)	Minimal
Idarubicin	Moderate
Ifosfamide	Moderate
Ifosfamide + doxorubicin*	High
Ifosfamide + etoposide*	High
Imatinib (oral)	Moderate
Intrathecal therapy (methotrexate, hydrocortisone & cytarabine)*	Moderate
Irinotecan	Moderate
Ixabepilone	Low
Lapatinib	Minimal
Lenalidomide	Minimal
Lomustine	Moderate
Mechlorethamine	High
Melphalan (oral low-dose)	Minimal

Antineoplastic Agent	Level of Emetic Risk
Melphalan > 50 mg/m^2	Moderate
Mercaptopurine (oral)	Minimal
Methotrexate > 50 mg/m^2 to < 250 mg/m^2	Low
Methotrexate ≤ 50 mg/m^2	Minimal
Methotrexate ≥ 12 g/m^{2*}	High
Methotrexate ≥ 250 mg/m^2 to < 12 g/m^2	Moderate
Methotrexate 5 g/m^2 + Doxorubicin	High
Methotrexate, hydrocortisone + cytarabine: Intrathecal therapy*	Moderate
Mitomycin	Low
Mitoxantrone	Low
Nelarabine	Minimal
Nilotinib	Low
Oxaliplatin > 75 mg/m^2	Moderate
Paclitaxel	Low
Paclitaxel-albumin	Low
Panitumumab	Minimal
Pemetrexed	Low
Pentostatin	Minimal
Procarbazine (oral)	High
Rituximab	Minimal
Sorafenib	Minimal
Streptozocin	High
Sunitinib	Minimal
Temozolomide (oral)	Moderate
Temsirolimus	Minimal
Teniposide	Low
Teniposide + cytarabine 300 mg/m^2 *	High
Thalidomide	Minimal
Thioguanine (oral)	Minimal
Thiotepa < 300 mg/m^2	Low
Thiotepa ≥ 300 mg/m^2 *	High
Topotecan	Low
Trastuzumab	Minimal
Valrubicin	Minimal
Vinblastine	Minimal
Vincristine	Minimal
Vindesine	Minimal
Vinorelbine	Minimal
Vinorelbine (oral)	Moderate
Vorinostat	Low

*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)

APPENDIX F: CONTENT EXPERT SURVEY

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.	**Strongly Agree**		**Neither Agree nor Disagree**		**Strongly Disagree**
a. The rationale for developing a guideline, as stated in the "*Introduction*" and "*Scope and Purpose*" sections of the draft guideline, is clear.	☐	☐	☐	☐	☐
b. There is a need for a Canadian practice guideline on Emetogenicity Classification.	☐	☐	☐	☐	☐
c. The literature search described in the draft guideline is complete (no key studies or guidelines were missed).	☐	☐	☐	☐	☐
d. The evidence described in the draft guideline is relevant.	☐	☐	☐	☐	☐
e. I agree with the methods used to summarize the evidence included in the draft guideline.	☐	☐	☐	☐	☐
f. The results of the studies described in the draft guideline are interpreted according to my understanding of the data.	☐	☐	☐	☐	☐
g. The draft recommendations are clear.	☐	☐	☐	☐	☐
h. I agree with the draft recommendations as stated.	☐	☐	☐	☐	☐
i. I would feel comfortable having these recommendations applied in my hospital.	☐	☐	☐	☐	☐

How likely would you be to adopt of these recommendations in your own practice?

Very Likely				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*.

_____

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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:

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

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

Very Likely			**Unsure**		**Not At All Likely**	
☐	☐	☐	☐	☐	☐	☐ **Not applicable**

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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