CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

Guidelines on Chemotherapy-induced Nausea and Vomiting in Pediatric Cancer Patients

COG Supportive Care Endorsed Guidelines

Click **here** to see all the COG Supportive Care Endorsed Guidelines.

This document summarizes four clinical practice guidelines on the topic of chemotherapy-induced nausea and vomiting:
I. The "Guideline for Classification of the Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Cancer Patients" (endorsed by the COG Supportive Care Guideline Committee in August 2014).
II. The "Guideline for the Prevention of Acute Nausea and Vomiting due to Antineoplastic Medication in Pediatric Cancer Patients" (endorsed by the COG Supportive Care Guideline Committee in January 2018).
III. The "Guideline for the Prevention and Treatment of Anticipatory Nausea and Vomiting due to Chemotherapy in Pediatric Cancer Patients" (endorsed by the COG Supportive Care Guideline Committee in August 2014) and
IV. The "Guideline for the Treatment of Breakthrough and Treatment of Refractory Chemotherapy-induced Nausea and Vomiting in Pediatric Cancer Patients" (endorsed by the COG Supportive Care Guideline Committee in October 2016).

I. Classification of Chemotherapy Emetogenicity

The "Guideline for Classification of the Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Cancer Patients" and implementation tools provided by the guideline developers can be found at: http://www.pogo.ca/healthcare/practiceguidelines/pogoemetogenicitycla/

A summary of the guideline is published in Pediatric Blood and Cancer 2011; 2011; 57:191-8. http://onlinelibrary.wiley.com/doi/10.1002/pbc.23114/pdf)

The purpose of this guideline is to provide an evidence-based approach to the assessment of the emetogenic potential of antineoplastic regimens in children. The recommendations of the endorsed guideline are presented below.

Summary of Recommendations for the Classification of Chemotherapy Emetogenicity

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
1. What risk of acute phase CINV do antineoplastic therapies present to children with cancer?	
The single antineoplastic agents provided in Table 1 have high, moderate, low or minimal emetogenic potential in children.	Strong recommendation Very low to low quality of evidence
2. Is the risk of CINV with multi-agent, single day antineoplastic therapy different than that of the most emetogenic antineoplastic given?	
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.	Strong recommendation Very low to low quality of evidence
3. Is the risk of CINV with multiple day antineoplastic therapy regimens different than that of the most emetogenic antineoplastic therapy given on any individual day?	
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.	Weak recommendation Very low quality of evidence

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 *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
Moderate Level of Emetic Risk (30-90% frequency of emesis in absence of prophylaxis)		
Aldesleukin > 12 to 15 million units/m^2 Amifostine > 300 mg/m^2 Arsenic trioxide Azacitidine Bendamustine Busulfan *Carmustine ≤ 250 mg/m^2 *Clofarabine *Cyclophosphamide < 1 g/m^2 Cyclophosphamide (oral)	Cytarabine > 200 mg to < 3 g/m^2 *Daunorubicin *Doxorubicin Epirubicin Etoposide (oral) Idarubicin Ifosfamide Imatinib (oral) *Intrathecal therapy (methotrexate, hydrocortisone & cytarabine)	Irinotecan Lomustine Melphalan > 50 mg/m^2 Methotrexate ≥ 250 mg to < 12 g/m^2 Oxaliplatin > 75 mg/m^2 Temozolomide (oral) Vinorelbine (oral)
Low Level of Emetic Risk (10-<30% frequency of emesis in absence of prophylaxis)		
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 to < 250 mg/m^2 Mitomycin Mitoxantrone Nilotinib	Paclitaxel Paclitaxel-albumin Pemetrexed Teniposide Thiotepa < 300 mg/m^2 Topotecan Vorinostat
Minimal (<10% frequency of emesis in absence of prophylaxis)		
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

* Pediatric evidence available Note: All agents given intravenously (IV) unless stated otherwise.

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	*Cytarabine 300 mg/m^2 + etoposide
*Cyclophosphamide + doxorubicin	*Cytarabine 300 mg/m^2 + teniposide
*Cyclophosphamide + epirubicin	*Doxorubicin + ifosfamide
*Cyclophosphamide + etoposide	Doxorubicin + methotrexate 5 g/m^2
*Cytarabine 150-200 mg/m^2 + daunorubicin	*Etoposide + ifosfamide

* Pediatric evidence available Note: All agents given intravenously (IV) unless stated otherwise.

II. **Prevention of Acute Chemotherapy-induced Nausea and Vomiting**

The "Guideline for the Prevention of Acute Nausea and Vomiting due to Antineoplastic Medication in Pediatric Cancer Patients" and the implementation tools provided by the guideline developers are available at: http://www.pogo.ca/healthcare/practiceguidelines/acuteainvguideline/

A summary of the guideline is published in Pediatric Blood and Cancer 2013; 60: 1073-82. http://onlinelibrary.wiley.com/doi/10.1002/pbc.24508/pdf and Pediatric Blood and Cancer 2017; 2017; 64: e26542. http://onlinelibrary.wiley.com/doi/10.1002/pbc.26542/epdf

The purpose of this guideline is to provide evidence-based recommendations for the prevention of acute chemotherapy-induced nausea and vomiting in children. The recommendations of the endorsed guideline are presented below.

Summary of Recommendations for the Prevention of Chemotherapy-induced Nausea and Vomiting (CINV)

RECOMMENDATIONS	**Strength of Recommendation and Quality of Evidence**
1. How is optimal control of acute CINV defined?	
We recommend that optimal control of acute CINV be defined as no vomiting, no retching, no nausea, no use of antiemetic agents other than those given for CINV prevention and no nausea-related change in the child's usual appetite and diet. This level of CINV control is to be achieved on each day that antineoplastic therapy is administered and for 24 hours after administration of the last antineoplastic agent of the antineoplastic therapy block	Strong recommendation Very low quality evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
2a. What pharmacological interventions provide optimal control of acute CINV in children receiving highly emetogenic chemotherapy (HEC)?	
We recommend that:	
• Children ≥ 6 months old receiving HEC which is *not* known or suspected to interact with aprepitant receive: *granisetron, ondansetron or palonosetron + dexamethasone + aprepitant*	Strong recommendation Moderate quality evidence
• Children < 6 months old receiving HEC receive: *granisetron, ondansetron or palonosetron + dexamethasone*	Strong recommendation Moderate quality evidence
• Children ≥ 6 months old receiving HEC which is known or suspected to interact with aprepitant receive: *granisetron, ondansetron or palonosetron + dexamethasone*	Strong recommendation Moderate quality evidence
• Children ≥ 6 months old receiving HEC which is *not* known or suspected to interact with aprepitant and who cannot receive dexamethasone for CINV prophylaxis receive: *palonosetron + aprepitant*	Strong recommendation Moderate quality evidence
We suggest that:	
• Children < 6 months old receiving HEC and who *cannot* receive dexamethasone for CINV prophylaxis receive: *palonosetron*	Weak recommendation Moderate quality evidence
• Children receiving HEC which is known or suspected to interact with aprepitant and who *cannot* receive dexamethasone for CINV prophylaxis receive: *palonosetron*	Weak recommendation Moderate quality evidence
2b. What pharmacological interventions provide optimal control of acute CINV in children receiving moderately emetogenic chemotherapy (MEC)?	
We recommend that:	
• Children receiving MEC receive: *granisetron, ondansetron or palonosetron + dexamethasone*	Strong recommendation Moderate quality evidence
We suggest that:	
• Children ≥ 6 months old receiving MEC who *cannot* receive dexamethasone for CINV prophylaxis receive: *granisetron, ondansetron or palonosetron + aprepitant*	Weak recommendation Moderate quality evidence
• Children < 6 months old receiving MEC who cannot receive dexamethasone for CINV prophylaxis receive: *palonosetron*	Weak recommendation Moderate quality evidence
• Children receiving MEC which is known or suspected to interact with aprepitant and who *cannot* receive dexamethasone for CINV prophylaxis receive: *palonosetron*	Weak recommendation Moderate quality evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
2c. What pharmacological interventions provide optimal control of acute CINV in children receiving antineoplastic agents of low emetic risk?	
We recommend that children receiving antineoplastic agents of low emetic risk receive: *ondansetron or granisetron*	Strong recommendation Moderate quality evidence
2d. What pharmacological interventions provide optimal control of acute CINV in children receiving antineoplastic agents of minimal emetic risk?	
We recommend that children receiving antineoplastic agents of low emetic risk receive: *no routine prophylaxis*	Strong recommendation Very low quality evidence
3. What adjunctive non-pharmacological interventions provide control of acute CINV in children receiving antineoplastic agents of any emetic risk?	
We suggest that acupuncture, acupressure, guided imagery, music therapy, progressive muscle relaxation and psycho-educational support and information may be effective in children receiving antineoplastic agents. Virtual reality may convey benefit. We suggest that the following dietary interventions may be effective: • eat smaller, more frequent meals; • reduce food aromas and other stimuli with strong odors; • avoid foods that are spicy, fatty or highly salty; • take antiemetics prior to meals so that the effect is present during and after meals; and • measures and foods (e.g. "comfort foods") that helped to minimize nausea in the past	Weak recommendation Very low quality evidence
4. What doses of antiemetic agents are known to be effective in children receiving antineoplastic agents?	
We suggest the following **aprepitant** dose for children ≥ 6 months old: *Day 1: 3 mg/kg/dose (maximum: 125mg) PO x 1;* *Days 2 and 3: 2 mg/kg/dose (maximum: 80mg) PO once daily*	Weak recommendation Moderate quality evidence
We suggest the following **dexamethasone** dose for children receiving highly emetogenic antineoplastic therapy: *6 mg/m^2/dose IV/PO q6h* If given concurrently with aprepitant, reduce dexamethasone dose by half. We recommend the following **dexamethasone** for children receiving moderately emetogenic antineoplastic therapy: *≤ 0.6m^2: 2mg/dose IV/PO q12h* *> 0.6m^2: 4mg/dose IV/PO q12h* If given concurrently with aprepitant, reduce dexamethasone dose by half	Weak recommendation Low quality evidence Strong recommendation Low quality evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
We recommend the following **IV granisetron** dose for children receiving highly emetogenic antineoplastic therapy: *40 mcg/kg/dose IV as a single daily dose*	Strong recommendation Low quality evidence
We recommend the following **IV granisetron** dose for children receiving moderately emetogenic antineoplastic therapy: *40 mcg/kg/dose IV as a single daily dose*	Strong recommendation Moderate quality evidence
We suggest the following **oral granisetron** dose for children receiving moderately emetogenic antineoplastic therapy: *40 mcg/kg/dose PO q12h*	Weak recommendation Low quality evidence
We recommend the following **IV granisetron** dose for children receiving antineoplastic therapy of low emetogenicity: *40 mcg/kg/dose IV as a single daily dose*	Strong recommendation Low quality evidence
We suggest the following **oral granisetron** dose for children receiving antineoplastic therapy of low emetogenicity: *40 mcg/kg/dose PO q12h*	Weak recommendation Low quality evidence
We recommend the following **ondansetron** dose for children receiving highly emetogenic antineoplastic therapy: *5 mg/m^2/dose (0.15 mg/kg/dose) IV/PO pre-therapy x 1 and then q8h*	Strong recommendation Moderate quality evidence
We recommend the following **ondansetron** dose for children receiving moderately emetogenic antineoplastic therapy: *5 mg/m^2/dose (0.15 mg/kg/dose; maximum 8 mg/dose) IV/PO pre-therapy x 1 and then q12h*	Strong recommendation Moderate quality evidence
We recommend the following **ondansetron** dose for children receiving therapy of low emetogenicity: *10 mg/m^2/dose (0.3 mg/kg/dose; maximum 16 mg/dose IV or 24 mg/dose PO) pre-therapy x 1*	Strong recommendation Low quality evidence
We suggest the following **palonosetron** dose for children: *1 month to < 17 years: 0.02 mg/kg/dose (maximum 1.5 mg) IV once pre-therapy* *≥ 17 years: 0.5 mg/dose PO once pre-therapy*	Weak recommendation Moderate quality evidence

III. **Prevention and Treatment of Anticipatory Chemotherapy-Induced Nausea and Vomiting**

The "Guideline for the Prevention and Treatment of Anticipatory Nausea and Vomiting due to Chemotherapy in Pediatric Cancer Patients" and the implementation tools provided by the guideline developers are available at: http://www.pogo.ca/healthcare/practiceguidelines/anticipatorycinv/

A summary of the guideline is published in Pediatric Blood and Cancer 2014; 61: 1506-12. http://onlinelibrary.wiley.com/doi/10.1002/pbc.25063/pdf

The purpose of this guideline is to provide evidence-based recommendations for the prevention and treatment of anticipatory chemotherapy-induced nausea and vomiting in children. The recommendations of the endorsed guideline are presented below.

Summary of Recommendations for the Prevention and Treatment of Anticipatory Chemotherapy-induced Nausea and Vomiting (CINV)

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
1. What approaches are recommended to prevent the development of anticipatory chemotherapy induced nausea and vomiting (CINV) in children?	
Control of acute and delayed CINV should be optimized for each child in order to minimize the risk of the child developing anticipatory CINV.	Strong recommendation Low quality evidence
2. What interventions are recommended to control anticipatory CINV in children who develop it?	
We suggest that psychological interventions such as hypnosis or systematic desensitization may be offered to children with anticipatory CINV.	Weak recommendation Moderate quality evidence
We suggest that lorazepam in a dose of 0.04 to 0.08 mg/kg/dose (maximum: 2 mg/dose) once at bedtime the night before chemotherapy and once the next day prior to administration of chemotherapy may be used to prevent or treat anticipatory CINV in children.	Weak recommendation Low quality evidence

IV. **Treatment of Breakthrough and Prevention of Refractory Chemotherapy-Induced Nausea and Vomiting**

The "Guideline for the Treatment of Breakthrough and Prevention of Refractory Chemotherapy-induced Nausea and Vomiting in Pediatric Cancer Patients" and the implementation tools provided by the guideline developers are available at: http://www.pogo.ca/healthcare/practiceguidelines/breakthrough-and-refractory-cinv/

A summary of the guideline is published in Pediatric Blood and Cancer 2016;63:1144–1151. http://onlinelibrary.wiley.com/doi/10.1002/pbc.25955/epdf

The purpose of this guideline is to provide evidence-based recommendations to optimize breakthrough and refractory CINV control in children. The recommendations of the endorsed guideline are presented below.

Summary of Recommendations for the Treatment of Breakthrough and the Prevention of Refractory Chemotherapy-induced Nausea and Vomiting

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
1. What interventions are recommended to treat breakthrough CINV in children? *Breakthrough CINV is defined as* nausea and/or vomiting presumed to be attributable to antineoplastic chemotherapy and with no other pathological cause that occurs during the acute or delayed phase despite CINV prophylaxis.	
For children receiving acute CINV prophylaxis recommended for minimally, low, or moderately emetogenic chemotherapy, clinicians should upgrade or escalate the acute CINV prophylaxis provided to that recommended for chemotherapy of the next higher level of emetogenic risk.	Strong recommendation Low quality evidence
For children receiving acute CINV prophylaxis recommended for highly emetogenic chemotherapy, we suggest that olanzapine be added to guideline-consistent CINV prophylaxis.	Weak recommendation Low quality evidence
For children receiving acute CINV prophylaxis recommended for highly emetogenic chemotherapy and who cannot receive olanzapine, we suggest that one of the following antiemetic agents be added to guideline-consistent CINV prophylaxis: • methotrimeprazine (also known as levomepromazine) or • metoclopramide (in children older than 1 year) Given the possibility of extrapyramidal reactions with these agents, the risks and benefits of their use should be weighed carefully and co-administration of prophylaxis aimed at preventing extrapyramidal symptoms (EPS) should be considered. Patients and families should also be educated about the possible occurrence of EPS.	Weak recommendation Very low quality evidence
2. What interventions are recommended to prevent CINV in children who have refractory CINV? *Refractory CINV is defined as* nausea and/or vomiting presumed to be attributable to antineoplastic chemotherapy and with no other pathological cause which occurs during the acute or delayed phase despite CINV prophylaxis in patients who have experienced breakthrough CINV in a previous chemotherapy block.	
For children receiving acute CINV prophylaxis recommended for minimally, low, or moderately emetogenic chemotherapy, clinicians should upgrade or escalate the acute CINV prophylaxis provided to that recommended for chemotherapy of the next higher level of emetogenic risk.	Strong recommendation Very low quality evidence

For children receiving acute CINV prophylaxis recommended for highly emetogenic chemotherapy, we suggest that the 5-HT3 antagonist given for CINV prophylaxis be changed from ondansetron or granisetron to palonosetron. In jurisdictions where palonosetron is not available, we suggest that granisetron be substituted for ondansetron.	Weak recommendation Very low quality evidence
For children experiencing refractory CINV despite initiation of previous recommendations and who have not previously received aprepitant because it is known or suspected to interact with the chemotherapeutic agent(s) being given, we suggest that the addition of aprepitant to acute CINV prophylaxis be considered.	Weak recommendation Low quality evidence
For children experiencing refractory CINV despite initiation of the previous recommendations, we suggest that one of the following interventions be added to the CINV prophylaxis provided:	
• interventions that were employed successfully for the treatment of breakthrough CINV in previous treatment blocks (olanzapine, methotrimeprazine or metoclopramide); or	Weak recommendation Very low quality evidence
• stimulation of Nei Gaun (P6) by means of acupressure or electroacupuncture.	Weak recommendation Very low quality evidence

Appendix 1: GRADE

Strength of Recommendations:

Strong Recommendation	When using GRADE, panels make strong recommendations when they are confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects.
Weak Recommendation	Weak recommendations indicate that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but the panel is less confident.

Strength of Recommendations Determinants:

Factor	Comment
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Costs (resource allocation)	The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted

Quality of Evidence

High Quality	Further research is very unlikely to change our confidence in the estimate of effect
Moderate Quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low Quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very Low Quality	Any estimate of effect is very uncertain

Guyatt, G.H., et al., *GRADE: an emerging consensus on rating quality of evidence and strength of recommendations.* BMJ, 2008; 336: 924-926.
Guyatt, G.H., et al., *GRADE: going from evidence to recommendations.* BMJ, 2008; 336: 1049-1051.