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

COG Supportive Care Endorsed Guidelines

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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 "<u>Guideline for the Treatment of Breakthrough and Treatment of Refractory Chemotherapy-induced Nausea and Vomiting in Pediatric Cancer Patients</u>" (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: <u>http://www.pogo.ca/healthcare/practiceguidelines/pogoemetogenicitycla/</u>

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.

RECOMMENDATIONS 1. What risk of acute phase CINV do antineoplastic therapies prese	Strength of Recommendation and Quality of Evidence ent 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 the 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.	erapy different than that of Strong recommendation Very low to low quality of evidence
agent in the combination to be given. 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 a	bsence of prophylaxis)	
Altretamine	*Cytarabine 3 g/m ² /dose	*Methotrexate \geq 12 g/m ²
*Carboplatin	Dacarbazine	Procarbazine (oral)
Carmustine > 250 mg/m ²	*Dactinomycin	Streptozocin
*Cisplatin	Mechlorethamine	*Thiotepa ≥ 300 mg/m ²
*Cyclophosphamide ≥1 g/m ²		
Moderate Level of Emetic Risk		
(30-90% frequency of emesis in	absence of prophylaxis)	
Aldesleukin > 12 to 15 million	Cytarabine > 200 mg to < 3 g/m ²	Irinotecan
units/m²	*Daunorubicin	Lomustine
Amifostine > 300 mg/m ²	*Doxorubicin	Melphalan > 50 mg/m ²
Arsenic trioxide	Epirubicin	Methotrexate \geq 250 mg to < 12
Azacitidine	Etoposide (oral)	g/m ²
Bendamustine	Idarubicin	Oxaliplatin > 75 mg/m ²
Busulfan	Ifosfamide	Temozolomide (oral)
*Carmustine ≤ 250 mg/m ²	Imatinib (oral)	Vinorelbine (oral)
*Clofarabine	*Intrathecal therapy	
*Cyclophosphamide < 1 g/m ²	(methotrexate, hydrocortisone &	
Cyclophosphamide (oral)	cytarabine)	
Low Level of Emetic Risk		
(10-<30% frequency of emesis in	n absence of prophylaxis)	
Amifostine $\leq 300 \text{ mg/m}^2$	Fludarabine (oral)	Paclitaxel
Amsacrine	5-Fluorouracil	Paclitaxel-albumin
Bexarotene	Gemcitabine	Pemetrexed
*Busulfan (oral)	Ixabepilone	Teniposide
Capecitabine	Methotrexate > 50 mg to < 250	Thiotepa < 300 mg/m^2
Cytarabine $\leq 200 \text{ mg/m}^2$	mg/m ²	Topotecan
Docetaxel	Mitomycin	Vorinostat
Doxorubicin (liposomal)	Mitoxantrone	Vormostat
Etoposide	Nilotinib	
Minimal		1
(<10% frequency of emesis in al	osence of prophylaxis)	
Alemtuzumab	Erlotinib	Sorafenib
Alpha interferon	Fludarabine	Sunitinib
Asparaginase (IM or IV)	Gefitinib	Temsirolimus
Bevacizumab	Gemtuzumab ozogamicin	Thalidomide
Bleomycin	Hydroxyurea (oral)	Thioguanine (oral)
Bortezomib	Lapatinib	Trastuzumab
Cetuximab	Lenalidomide	Valrubicin
Chlorambucil (oral)	Melphalan (oral low-dose)	Vinblastine
Cladribine (2-	Mercaptopurine (oral)	Vincristine
chlorodeoxyadenosine)	Methotrexate $\leq 50 \text{ mg/m}^2$	Vindesine
Decitabine	Nelarabine	Vinorelbine
Denileukin diftitox	Panitumumab	
Dasatinib	Pentostatin	
Dexrazoxane	Rituximab	

* 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 *Cyclophosphamide + doxorubicin	*Cytarabine 300 mg/m ² + etoposide *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. <u>http://onlinelibrary.wiley.com/doi/10.1002/pbc.24508/pdf</u> and Pediatric Blood and Cancer 2017; 2017; 64: e26542. <u>http://onlinelibrary.wiley.com/doi/10.1002/pbc.26542/epdf</u>

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	Strong recommendation
vomiting, no retching, no nausea, no use of antiemetic agents other	Very low quality evidence
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	

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

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
2c. What pharmacological interventions provide optimal control of ac 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 ac antineoplastic agents of minimal emetic risk?	cute CINV in children receiving
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 contractions antineoplastic agents of any emetic risk?	rol of acute CINV in children
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.	Weak recommendation Very low quality evidence
 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 	
4. What doses of antiemetic agents are known to be effective in chil agents?	dren receiving antineoplastic
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.	Weak recommendation Low quality evidence
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	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:	Strong recommendation
40 mcg/kg/dose IV as a single daily dose	Low quality evidence
We recommend the following IV granisetron dose for children receiving moderately emetogenic antineoplastic therapy:	Strong recommendation
40 mcg/kg/dose IV as a single daily dose	Moderate quality evidence
We suggest the following oral granisetron dose for children receiving moderately emetogenic antineoplastic therapy:	Weak recommendation
40 mcg/kg/dose PO q12h	Low quality evidence
We recommend the following IV granisetron dose for children receiving antineoplastic therapy of low emetogenicity:	Strong recommendation
40 mcg/kg/dose IV as a single daily dose	Low quality evidence
We suggest the following oral granisetron dose for children receiving antineoplastic therapy of low emetogenicity:	Weak recommendation
40 mcg/kg/dose PO q12h	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: <u>http://www.pogo.ca/healthcare/practiceguidelines/anticipatorycinv/</u>

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 Chemotherapyinduced Nausea and Vomiting (CINV)

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
1. What approaches are recommended to prevent the development induced nausea and vomiting (CINV) in children?	of anticipatory chemotherapy
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 CIN	V 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: <u>http://www.pogo.ca/healthcare/practiceguidelines/breakthrough-and-refractory-cinv/</u>

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

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 <i>Breakthrough CINV is defined as</i> nausea and/or vomiting presumed to I antineoplastic chemotherapy and with no other pathological cause that delayed phase despite CINV prophylaxis.	be attributable to t occurs during the acute or
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 we <i>Refractory CINV is defined as</i> nausea and/or vomiting presumed to be a chemotherapy and with no other pathological cause which occurs durin despite CINV prophylaxis in patients who have experienced breakthrout chemotherapy block.	attributable to antineoplastic ng the acute or delayed phase
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	Weak recommendation
highly emetogenic chemotherapy, we suggest that the 5-HT3	Very low quality evidence
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.	
For children experiencing refractory CINV despite initiation of	Weak recommendation
previous recommendations and who have not previously received	Low quality evidence
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.	
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:	
) M / o o ly wo o o more o molestic m
• interventions that were employed successfully for the treatment	Weak recommendation
of breakthrough CINV in previous treatment blocks (olanzapine,	Very low quality evidence
methotrimeprazine or metoclopramide); or	
 stimulation of Nei Gaun (P6) by means of acupressure or 	Weak recommendation
electroacupuncture.	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	The larger the difference between the desirable and undesirable
and undesirable effects	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.