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

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This document summarizes four clinical practice guidelines on the topic of chemotherapy-induced nausea and vomiting:
I. The "Classification of the Acute Emetogenicity of Chemotherapy in Pediatric Patients: A Clinical Practice Guideline" (endorsed by the COG Supportive Care Guideline Committee in August 2019).
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 "Classification of the Acute Emetogenicity of Chemotherapy in Pediatric Patients: A Clinical Practice Guideline" developed by the Pediatric Oncology Group of Ontario was endorsed by the COG Supportive Care Guideline Committee in August 2019.

The source guideline is published (Paw Cho Sing E, Robinson PD, Flank J et al. Pediatr Blood Cancer. 2019; 66: e27646.) and is available at https://onlinelibrary.wiley.com/doi/epdf/10.1002/pbc.27646. It is an update of an earlier guideline that was published in 2011.

The purpose of this guideline is to provide evidence-based recommendations regarding the acute emetic potential of chemotherapy in pediatric oncology patients aged 1 month to 18 years. 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. Which chemotherapy regimens are highly emetogenic?	
Single-agent regimens: Asparaginase (*Erwinia*) IV ≥ 20,000 IU/m^2/dose Busulfan IV ≥ 0.8mg/kg/dose Busulfan PO ≥ 1mg/kg/dose Carboplatin IV ≥ 175 mg/m^2/dose Cisplatin IV ≥ 12 mg/m^2/dose Cyclophosphamide IV ≥ 1,200 mg/m^2/dose Cytarabine IV ≥ 3g/m^2/day Dactinomycin IV ≥ 1.35 mg/m^2/dose Doxorubicin IV ≥ 30 mg/m^2/dose Idarubicin PO ≥ 30 mg/m^2/dose Melphalan IV Methotrexate IV ≥ 12 g/m^2/dose	Strong recommendation Very low to high quality of evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
Multiple-agent regimens: Cyclophosphamide ≥ 600 mg/m^2/dose + dactinomycin ≥ 1 mg/m^2/dose Cyclophosphamide ≥ 400 mg/m^2/dose + doxorubicin ≥ 40 mg/m^2/dose Cytarabine IV ≥ 90 mg/m^2/dose + methotrexate IV ≥ 150 mg/m^2/dose Cytarabine IV + teniposide IV Dacarbazine IV ≥ 250 mg/m^2/dose + doxorubicin IV ≥ 60 mg/m^2/dose Dactinomycin IV ≥ 900 µg/m^2/dose + ifosfamide IV ≥ 3 g/m^2/dose Etoposide IV ≥ 60 mg/m^2/dose + ifosfamide IV ≥ 1.2 g/m^2/dose Etoposide IV ≥ 250 mg/m^2/dose + thiotepa IV ≥ 300 mg/m^2/dose	
2. Which single-agent and multiple-agent chemotherapy regimens are moderately emetogenic?	
Single-agent regimens: Cyclophosphamide IV 1000 mg/m^2/dose Cytarabine IV 75 mg/m^2/dose Dactinomycin IV 10 µg/kg/dose Doxorubicin IV 25 mg/m^2/dose Gemtuzumab IV 3–9mg/m^2/dose Imatinib PO > 260 mg/m^2/day Interferon alpha IV 15–30 million U/m^2/day Ixabepilone IV 3–10 mg/m^2/dose Methotrexate IV 5 g/m^2/dose Methotrexate IT Topotecan PO 0.4–2.3 mg/m^2/day Multiple-agent regimens: Cytarabine IV 100 mg/m^2/dose + daunorubicin IV 45 mg/m^2/dose + etoposide IV 100 mg/m^2/dose + prednisolone PO + thioguanine PO 80mg/m^2/dose Cytarabine 60 or 90 mg/m^2/dose + methotrexate 120 mg/m^2/dose Liposomal doxorubicin IV 20–50 mg/m^2/dose + topotecan PO 0.6mg/m^2/day	Strong recommendation Very low to high quality of evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence
3. Which single-agent and multiple-agent chemotherapy regimens are of low emetogenicity?	
Single-agent regimens: Cyclophosphamide IV 500 mg/m^2/dose Cyclophosphamide PO2–3 mg/kg/dose Dasatinib PO 60–120 mg/m^2/dose Erlotinib PO 35–150 mg/m^2/day Everolimus PO 0.8–9mg/m^2/day Gefitinib PO 150–500 mg/m^2/day Imatinib PO 260 mg/m^2/day Mafosfamide IT 1–6.5 mg/dose Melphalan PO 0.2 mg/kg/dose Mercaptopurine PO ≤ 4.2mg/kg/dose Methotrexate 38–83 mg/m^2/dose IV Mitoxantrone IV ≤ 33 mg/m^2/dose Procarbazine PO 50–100 mg/m^2/day Ruxolitinib PO 15–21 mg/m^2/dose Selumetinib PO 20–30 mg/m^2/dose Sorafenib PO 150–325 mg/m^2/dose Temozolomide PO 200 mg/m^2/dose Multiple-agent regimens: Cytarabine IV 60 mg/m^2/dose + methotrexate IV 90 mg/m^2/dose	Strong recommendation Very low to moderate quality of evidence
4. Which single-agent and multiple-agent chemotherapy regimens are minimally emetogenic?	
Single-agent regimens: Asparaginase (*E. coli*) IM ≤ 6000 IU/m^2/dose Asparaginase (*Erwinia*) IM ≤ 25 000 IU/m^2/dose Chlorambucil ≤ 0.2mg/kg/day PO Doxorubicin IV 10 mg/m^2/dose Liposomal doxorubicin IV ≤ 50 mg/m^2/dose Mercaptopurine PO ≤ 4.2mg/kg/dose Methotrexate PO/SC ≤ 10 mg/m^2/dose Pracinostat PO 25–45 mg/m^2/dose Vincristine IV ≤ 1.5mg/m^2/dose Multiple-agent regimens: Cisplatin ≤ 60 mg/m^2/dose intra-arterially + doxorubicin ≤ 30 mg/m^2/dose intra-arterially Cisplatin ≤ 60 mg/m^2/dose intra-arterially + pirarubicin ≤ 30 mg/m^2/dose intra-arterially Mercaptopurine PO ≤ 2.5mg/kg/dose + methotrexate PO ≤ 0.1mg/kg/day	Strong recommendation Very low to low quality of evidence

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" developed by the Pediatric Oncology Group of Ontario was endorsed by the COG in January 2018.

The source guideline and its focused update are published (Dupuis LL, Boodhan S, Holdsworth M, et al. Pediatr Blood Cancer. 2013; 60: 1073-82. and Patel P, Robinson PD, Thackray J, et al. Pediatr Blood Cancer. 2017; 2017; 64: e26542.) and are available at:
http://onlinelibrary.wiley.com/doi/10.1002/pbc.24508/pdf and
http://onlinelibrary.wiley.com/doi/10.1002/pbc.26542/epdf

Implementation tools developed by the guideline developer are available at:
https://www.pogo.ca/healthcare/practiceguidelines/chemotherapy-induced-nausea-and-vomiting-cinv/

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 Acute 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 minimal 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" was endorsed by the COG in August 2014.

The source guideline is published (Flank J, Robinson PD, Boodhan S, et al. Pediatr Blood Cancer 2014; 61: 1506-12.) and is available at: 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" was endorsed by the COG in October 2016.

The source guideline is published (Flank J, Robinson PD, Holdsworth M, et al. Pediatr Blood Cancer 2016;63:1144–1151.) and is available at: 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

RECOMMENDATIONS	Strength of Recommendation and Quality of 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.