CHILDREN'S ONCOLOGY GROUP

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 "Antiemetics: ASCO Guideline Update" (endorsed by the COG Supportive Care Guideline Committee in December 2020)
III. The "Prevention of acute and delayed chemotherapy-induced nausea and vomiting in pediatric cancer patients: A clinical practice guideline" (endorsed by the COG Supportive Care Guideline Committee in February 2023) and
IV. The "Prevention and treatment of anticipatory chemotherapy-induced nausea and vomiting in pediatric cancer patients and hematopoietic stem cell recipients: Clinical practice guideline update" (endorsed by the COG Supportive Care Guideline Committee in July 2021).

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

*See Appendix 1

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

The "Antiemetics: ASCO Update" developed by the American Society of Clinical Oncology was endorsed by the COG in December 2020.

The source guideline is published (Hesketh P, Kris MG, Basch E et al. JCO 2020; 38 (24): 2782-97.) and is available at: https://ascopubs.org/doi/10.1200/JCO.20.01296

The "Prevention of acute and delayed chemotherapy-induced nausea and vomiting in pediatric cancer patients: A clinical practice guideline" developed by the Pediatric Oncology Group of Ontario was endorsed by the COG in February 2023.

The source guideline is published (Patel P, Robinson PD, Cohen M, et al. Prevention of acute and delayed chemotherapy-induced nausea and vomiting in pediatric cancer patients: A clinical practice guideline. Pediatr Blood Cancer. 2022 Dec;69(12):e30001) and is available at: https://onlinelibrary.wiley.com/doi/epdf/10.1002/pbc.30001

The purpose of these guidelines is to provide evidence-based recommendations for the prevention of acute chemotherapy-induced nausea and vomiting in children. The recommendations of the endorsed guidelines 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. In pediatric patients receiving highly emetogenic chemotherapy (HEC), what strategies are recommended to prevent acute CINV?	
a. Use a 5HT3RA + dexamethasone + (fos)aprepitant	Strong recommendation High quality evidence
b. Use palonosetron + dexamethasone in patients unable to receive (fos)aprepitant	Strong recommendation Moderate quality evidence
c. Use palonosetron + (fos)aprepitant in patients unable to receive dexamethasone	Strong recommendation Low quality evidence
d. Use palonosetron in patients unable to receive dexamethasone + (fos)aprepitant	Strong recommendation Moderate quality evidence
e. Consider adding olanzapine to other CPG-consistent antiemetics	Conditional recommendation Moderate quality evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence*
2. In pediatric patients receiving moderately emetogenic chemotherapy (MEC), what strategies are recommended to prevent acute CINV?	
a. Use a 5HT3RA + dexamethasone	Strong recommendation Moderate quality evidence
b. Use a 5HT3RA + (fos)aprepitant in patients unable to receive dexamethasone	Strong recommendation Low quality evidence
c. Use a 5HT3RA in patients unable to receive dexamethasone + (fos)aprepitant	Strong recommendation Low quality evidence
d. Consider using palonosetron as the preferred 5HT3RA in patients unable to receive dexamethasone + (fos)aprepitant	Conditional recommendation Low quality evidence
e. Consider adding olanzapine to other CPG-consistent antiemetics in patients unable to receive dexamethasone + (fos)aprepitant	Conditional recommendation Low quality evidence
3. In pediatric patients receiving low emetogenic chemotherapy (LEC), what strategies are recommended to prevent acute CINV?	
a. Use a 5HT3RA	Strong recommendation Low quality evidence
4. In pediatric patients receiving minimally emetogenic chemotherapy (minEC), what strategies are recommended to prevent acute CINV?	
a. Do not use prophylaxis routinely	Strong recommendation Very low quality evidence

CINV, chemotherapy-induced nausea and vomiting; 5HT3RA, serotonin-3 receptor antagonist; (fos)aprepitant, IV fosaprepitant or oral aprepitant
*See Appendix 1

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

The "Prevention of acute and delayed chemotherapy-induced nausea and vomiting in pediatric cancer patients: A clinical practice guideline" developed by the Pediatric Oncology Group of Ontario was endorsed by the COG in February 2023.

The source guideline is published (Patel P, Robinson PD, Cohen M, et al. Prevention of acute and delayed chemotherapy-induced nausea and vomiting in pediatric cancer patients: A clinical practice guideline. Pediatr Blood Cancer. 2022 Dec;69(12):e30001) and is available at: https://onlinelibrary.wiley.com/doi/epdf/10.1002/pbc.30001

The purpose of this guideline is to provide evidence-based guidance on strategies for delayed chemotherapy-induced nausea and vomiting prevention. The recommendations of the endorsed guideline are presented below.

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

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence*
1. In pediatric patients receiving highly emetogenic chemotherapy (HEC), what strategies are recommended to prevent delayed CINV?	
a. Use palonosetron in the acute phase as the preferred 5HT3RA in patients at high risk of delayed phase CINV	Strong recommendation Moderate quality evidence
b. Use oral aprepitant in the delayed phase, if (fos)aprepitant started in the acute phase	Strong recommendation High quality evidence
c. Add dexamethasone in the delayed phase in patients who received granisetron or ondansetron in the acute phase	Strong recommendation Moderate quality evidence
d. Consider adding dexamethasone in the delayed phase in patients who received palonosetron in the acute phase	Conditional recommendation Moderate quality evidence
e. Use dexamethasone in the delayed phase in patients unable to receive oral aprepitant	Strong recommendation Moderate quality evidence
f. Continue olanzapine in the delayed phase, if started in the acute phase	Strong recommendation Moderate quality evidence
g. Do not use 5HT3RAs in the delayed phase	Strong recommendation Low quality evidence
2. In pediatric patients receiving moderately emetogenic chemotherapy (MEC), what strategies are recommended to prevent delayed CINV?	
a. Consider using dexamethasone in the delayed phase	Conditional recommendation Low quality evidence
b. Continue oral aprepitant in the delayed phase in patients receiving single-day chemotherapy who received (fos)aprepitant in the acute phase	Strong recommendation Moderate quality evidence
c. Consider not using oral aprepitant in the delayed phase in patients receiving multi-day chemotherapy (≥ 3 days) who received (fos)aprepitant in the acute phase	Conditional recommendation Low quality evidence
d. Continue olanzapine in the delayed phase, if started in the acute phase	Strong recommendation Low quality evidence
3. In pediatric patients receiving low emetogenic chemotherapy (LEC), what strategies are recommended to prevent delayed CINV?	
a. Do not use prophylaxis routinely in the delayed phase	Strong recommendation Very low quality evidence
4. In pediatric patients receiving minimally emetogenic chemotherapy (minEC), what strategies are recommended to prevent delayed CINV?	
a. Do not use prophylaxis routinely in the delayed phase	Strong recommendation Very low quality evidence

CINV, chemotherapy-induced nausea and vomiting; 5HT3RA, serotonin-3 receptor antagonist; (fos)aprepitant, IV fosaprepitant or oral aprepitant

*See Appendix 1

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

The "Prevention and treatment of anticipatory chemotherapy-induced nausea and vomiting in pediatric cancer patients and hematopoietic stem cell recipients: Clinical practice guideline update" was endorsed by the COG in July 2021.
The source guideline is published (Patel P, Robinson PD, Devine KA, et al. Pediatr Blood Cancer 2021; e28947.) and is available at: https://onlinelibrary.wiley.com/doi/epdf/10.1002/pbc.28947

The purpose of this guideline is to provide those caring for pediatric oncology or hematopoietic stem cell recipients up to 18 years of age with updated recommendations for the prevention of anticipatory CINV. 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 strategies are recommended for primary prevention of anticipatory CINV in pediatric patients?	
1.1 Optimize acute and delayed CINV control to minimize the risk of anticipatory CINV *Remarks:* This recommendation places high value on the consistent evidence that a history of acute or delayed CINV is a risk factor for anticipatory CINV. This recommendation also considers the other benefits of optimized acute or delayed CINV control including improved quality of life and the low risk of toxicities anticipated with CPG-consistent antiemetics.	Strong recommendation Moderate- quality evidence
2. What strategies are recommended for secondary prevention of anticipatory CINV in pediatric patients?	
2.1: Consider offering cooperative patients one or more of the following nonpharmacological interventions for secondary prevention of anticipatory CINV: hypnosis, systematic desensitization, or relaxation techniques. *Remarks*: This recommendation places a high value on the minimal risks associated with these interventions. A conditional recommendation was made as the supporting evidence was limited to a small number of studies, the direct pediatric experience is scant and reports of the benefits of these interventions are inconsistent.	Conditional recommendation Low-quality evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence*
2.2 Consider using lorazepam for secondary prevention of anticipatory CINV. *Remarks*: This recommendation remained unchanged from the 2014 CPG. It places a high value on the limited data demonstrating improved anticipatory CINV control in adults given benzodiazepines. It is a conditional recommendation because there is no direct pediatric evidence among included studies describing the use of benzodiazepines for this purpose.	Conditional recommendation Very low-quality evidence
2.3 We suggest that ginger not be used routinely for secondary prevention of anticipatory CINV. *Remarks:* The panel made a conditional recommendation against the routine use of ginger given inconsistent study results in adult patients and the absence of pediatric data to support the use of ginger for this purpose. The panel also appreciated that the ginger formulations evaluated in included studies may not be comparable because doses of the components thought to be medically active are not uniformly reported.	Conditional recommendation Low-quality evidence
2.4 Do not use clonidine for secondary prevention of anticipatory CINV. *Remarks*: The panel made a strong recommendation against the use of clonidine given its poor safety profile, lack of clear benefit, and lack of direct data for its use in pediatric patients for anticipatory CINV prevention.	Strong recommendation Low-quality evidence
3. What strategies are recommended for acute treatment of anticipatory CINV in pediatric patients?	
No recommendation can be made. *Remarks:* No identified study directly evaluated an intervention aimed at the treatment of anticipatory CINV. The evidence describing primary and secondary anticipatory CINV prevention could not be extrapolated to make a recommendation.	

*See Appendix 1

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/Conditional 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.