Agency for Healthcare Research and Quality
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NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Guideline for the treatment of breakthrough and the prevention of refractory chemotherapy-induced nausea and vomiting in children with cancer.

Bibliographic Source(s)

Flank J, Robinson PD, Holdsworth M, Phillips R, Portwine C, Gibson P, Maan C, Stefin N, Sung L, Dupuis LL. Guideline for the treatment of breakthrough and the prevention of refractory chemotherapy-induced nausea and vomiting in children with cancer. Pediatr Blood Cancer. 2016 Jul;63(7):1144-51. [39 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Strength of recommendations (Strong, Weak) and quality of evidence (High, Moderate, Low, Very Low) are defined at the end of the "Major Recommendations" field.

Health question #1: What interventions are recommended to treat breakthrough chemotherapy-induced nausea and vomiting (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.

Recommendations

- *Recommendation 1.1*: 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)
- *Recommendation 1.2*: For children receiving acute CINV prophylaxis recommended for highly emetogenic chemotherapy, the Guideline Panel suggests that olanzapine be added to guideline-consistent CINV prophylaxis. (Weak Recommendation, Low Quality Evidence)
- *Recommendation 1.3*: For children receiving acute CINV prophylaxis recommended for highly emetogenic chemotherapy and who cannot receive olanzapine, the Guideline Panel suggests 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)

(Weak Recommendation, Very Low Quality Evidence)

Given the possibility of extrapyramidal reactions with these agents, the risks and benefits of their use should be weighed carefully and coadministration of prophylaxis aimed at preventing extrapyramidal symptoms (EPS) should be considered. Patients and families should also be educated about the possible occurrence of EPS.

Health question #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.

Recommendations

- *Recommendation 2.1*: 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)
- *Recommendation 2.2*: For children receiving acute CINV prophylaxis recommended for highly emetogenic chemotherapy, the Guideline Panel suggests that the 5-HT3 (serotonin) antagonist given for CINV prophylaxis be changed from ondansetron or granisetron to palonosetron. In jurisdictions where palonosetron is not available, the Guideline Panel suggests that granisetron be substituted for ondansetron. (Weak Recommendation, Very Low Quality of Evidence)
- *Recommendation 2.3*: 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, the Guideline Panel suggests that the addition of aprepitant to acute CINV prophylaxis be considered. (Weak Recommendation, Low Quality Evidence)
- *Recommendation 2.4*: For children experiencing refractory CINV despite initiation of the previous recommendations, the Guideline Panel suggests 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) (Weak Recommendation, Very Low Quality Evidence); or
  - Stimulation of Nei Gaun (P6) by means of acupressure or electroacupuncture (Weak Recommendation, Very Low Quality Evidence)

Definitions

Quality of Evidence

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

Strength of Recommendations

Strong Recommendation	When using Grading of Recommendations Assessment, Development and Evaluation (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.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Breakthrough and refractory chemotherapy-induced nausea and vomiting (CINV)

Guideline Category

Prevention

Treatment

Clinical Specialty

Oncology

Pediatrics

Preventive Medicine

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To optimize breakthrough and refractory chemotherapy-induced nausea and vomiting (CINV) control in children

Note: For the purpose of this guideline, optimal control of breakthrough CINV is defined as acute relief of nausea or vomiting during the current chemotherapy block. Optimal control of refractory CINV is 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.

Target Population

Children aged 1 month to 18 years receiving chemotherapy

Interventions and Practices Considered

Treatment

1. Upgrading or escalating acute chemotherapy-induced nausea and vomiting (CINV) prophylaxis
2. Addition of olanzapine to guideline-consistent CINV prophylaxis
3. Addition of methotrimeprazine (also known as levomepromazine) to guideline-consistent CINV prophylaxis
4. Addition of metoclopramide (in children older than 1 year) to guideline-consistent CINV prophylaxis
5. Educating patients and families about extrapyramidal symptoms (EPS)

Prevention

1. Upgrading or escalating acute CINV prophylaxis
2. Changing from ondansetron or granisetron to palonosetron

3. Addition of aprepitant to acute CINV prophylaxis
4. Addition of olanzapine, methotrimeprazine or metoclopramide
5. Stimulation of Nei Gaun (P6) by means of acupressure or electroacupuncture

Major Outcomes Considered

- Proportion of patients experiencing complete control of chemotherapy-induced nausea and vomiting (CINV) in refractory patients
- Response to the first dose of the breakthrough treatment (ideally within the first 24 hr after administration) described as a proportion of patients experiencing complete control or/and during the remainder of the phase in question (acute/delayed)
- Adverse effects associated with the use of antiemetics

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Systematic Literature Searches

In March 2015, computerized searches (see Supplementary Table SI [see the "Availability of Companion Documents" field]) were performed with the assistance of a library scientist to identify guidelines that could be endorsed for the treatment of breakthrough chemotherapy-induced nausea and vomiting (CINV) and for the prevention of refractory CINV in children. A total of 4,451 citations were identified and screened. Since none met the inclusion criteria (see Table II in the original guideline document) for endorsement assessment, the guideline panel proceeded to develop a *de novo* guideline. Systematic reviews of primary studies evaluating interventions for the treatment of breakthrough CINV and the prevention of refractory CINV were conducted.

Evidence Identification and Synthesis

The Guideline Development Group searched for primary studies pertinent to the guideline topics (see Supplementary Tables SII and SIII [see the "Availability of Companion Documents" field]) as of March 13, 2015. Eligibility was not restricted by age or language. All primary study designs, except single case reports, were eligible. Citations were screened independently by two reviewers. Conflicts were resolved by a third. Potentially relevant citations were included for full-text screening. Two reviewers independently evaluated the full-text papers to determine whether they met the inclusion criteria (see Table II in the original guideline document). Disagreements were resolved by a third reviewer.

During the guideline development process, it became apparent that understanding the safety of specific medications in children with cancer was required to better inform recommendations. Therefore, systematic reviews evaluating the safety of metoclopramide and prochlorperazine were undertaken, and an existing systematic review of the safety of olanzapine in children was considered by the panel. Primary studies relating to the safety of methotrimeprazine in children were also searched (see Supplementary Table SIII [see the "Availability of Companion Documents" field]) as of March 9, 2015 with the assistance of a library scientist. Citations were screened, full-text papers were evaluated to determine if they met the inclusion criteria (see Table II in the original guideline document).

Number of Source Documents

A total of 4,654 references were identified from the database searches. Of these, 116 papers were reviewed in full text and 59 (breakthrough chemotherapy-induced nausea and vomiting [CINV]: 13; refractory CINV: 46) satisfied the eligibility criteria (see Figure 1 in the original guideline document for a flowchart of the literature identification process) and were included in the systematic review.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence

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

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Evidence summary tables were compiled. See the supplementary materials (see the "Availability of Companion Documents" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Health Questions

The guideline sought to answer the following health questions:

1. What interventions are recommended to treat breakthrough chemotherapy-induced nausea and vomiting (CINV) in children?
2. What interventions are recommended to prevent CINV in children who have refractory CINV?

Guideline Panel and Development of Clinical Questions

Guideline panel members were chosen to represent inter-professional staff from Pediatric Oncology Group of Ontario centers and from internationally recognized experts in pediatric supportive care. Once chosen, the panel members developed the specific health questions (see above) to be addressed by this guideline.

Evidence Synthesis

Decisions were taken through panel discussions; any differences in opinion were resolved by consensus. The quality of evidence and strength of recommendations were assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. In formulating recommendations, health benefits, adverse effects, and risks were explicitly considered.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Strong Recommendation	When using Grading of Recommendations Assessment, Development and Evaluation (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.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

External Review and Consultation Process

The draft guideline underwent a two-stage external review: first by international experts in chemotherapy-induced nausea and vomiting (CINV) and then by stakeholders from the Ontario pediatric oncology community. Six content experts provided a review; their comments were discussed in detail by the panel and a decision on each point was taken by consensus. Ten Ontario pediatric oncology stakeholders also provided comments. These identified the need to develop guideline implementation tools.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Optimized the control of breakthrough and refractory chemotherapy-induced nausea and vomiting (CINV) in children

Potential Harms

- No clinically significant adverse effects were reported in either study that evaluated olanzapine for the treatment of breakthrough chemotherapy-induced nausea and vomiting (CINV) in adults. Dizziness, fatigue, and dyspepsia, described as mild and tolerable, were reported in one study.
- In a systematic review and meta-analysis, weight gain and sedation (78% [95% confidence interval (CI): 63% to 95%] and 48% [95% CI: 35% to 67%], respectively) were commonly associated with the use of olanzapine in children less than 13 years old. Extrapyramidal symptoms (EPS) and electrocardiograph abnormalities were reported less frequently (9% [95% CI: 4% to 21%] and 14% [95% CI: 7% to 26%], respectively). Most adverse effects associated with olanzapine use were of minor clinical significance; no fatalities attributable to olanzapine were identified.
- In one study, drowsiness, dry mouth, and constipation were the most commonly reported adverse effects of methotrimeprazine in adult psychiatric patients in one study. Sedation (12/32 patients), hypotension (8/32), and induration at the site of methotrimeprazine administration (32/32) were the most commonly reported adverse effects experienced by patients included in that study.
- Four studies (two retrospective reviews, one case series, and one case report) involving 30 children were included in a systematic review of

the safety of methotrimeprazine in children (see Supplementary Table SV [see the "Availability of Companion Documents" field]). No persistent adverse effects or fatalities were attributable to methotrimeprazine in these studies.
- In a recent systematic review and meta-analysis of adverse effects of metoclopramide in children, the mean proportion of children reported to have EPS was 9% (95% CI: 5% to 17%) or diarrhea was 6% (95% CI: 3% to 9%). In single dose and multiple-dose metoclopramide studies, the mean proportion of children reported to experience sedation was 2% (95% CI: 1% to 5%) and 6% (95% CI: 3% to 12%), respectively.
- The most commonly reported adverse effects of palonosetron reported by patients in one study were constipation and anxiety; no patient experienced severe toxicity.
- Aprepitant is a cytochrome P450 3A4 (CYP3A4) substrate and an inhibitor of cytochrome P450 2C9/8 (CYP2C9/8) and cytochrome P450 2C19 (CYP2C19). As a result, it may potentially interact with medications, including chemotherapy, metabolized via these pathways. Interactions with chemotherapy that may lead to an increased risk of short- and long-term toxicity are of primary concern.
- The potential improvement in CINV control offered by the addition of aprepitant should be weighed against the short- and long-term toxicities resulting from potential interactions with chemotherapy. It is essential to include the patient, when appropriate, and family in this discussion so their values can be incorporated into the decision-making process. The relative risks of aprepitant (potential for drug interaction with chemotherapy and altered chemotherapy exposure) and benefits (CINV control) should be determined on a case-by-case basis.

Contraindications

Contraindications

- Olanzapine should be avoided in patients receiving cytochrome P450 1A2 (CYP1A2) inducers (e.g., carbamazepine, rifampin) or inhibitors (e.g. ciprofloxacin, fluvoxamine) as olanzapine is primarily metabolized via this enzymatic pathway.
- Since Health Canada and the European Medicines Agency have recently issued warnings regarding the risk of extrapyramidal symptoms (EPS) in young children receiving metoclopramide, the panel recommends that metoclopramide be avoided in children less than 1-year old.

Qualifying Statements

Qualifying Statements

These recommendations are based on a systematic review of the literature. However, there are many gaps in the available evidence. Optimization of chemotherapy-induced nausea and vomiting (CINV) control in children requires delivery of care based on the best available evidence and the prospective evaluation of both new and old antiemetic agents.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2016 Jul

Guideline Developer(s)

Pediatric Oncology Group of Ontario - Professional Association

Source(s) of Funding

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Guideline Committee

Guideline Panel

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Conflicts of interest: Nothing to declare

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Pediatric Blood and Cancer Web site .

Availability of Companion Documents

Supplementary materials are available from the Pediatric Oncology Group of Ontario Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on December 21, 2016. The information was not verified by the guideline developer.

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