Guideline for the Treatment of Breakthrough and the Prevention of Refractory Chemotherapy-Induced Nausea and Vomiting in Children With Cancer

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This clinical practice guideline provides an approach to the treatment of breakthrough chemotherapy-induced nausea and vomiting (CINV) and the prevention of refractory CINV in children. It was developed by an international, interprofessional panel and is based on systematic literature reviews. Evidence-based interventions for the treatment of breakthrough and prophylaxis of refractory CINV are recommended. Gaps in the evidence used to support the recommendations made in this clinical practice guideline were identified. The contribution of these recommendations to breakthrough and refractory CINV control in children requires prospective evaluation. Pediatr Blood Cancer 0000;00:000–000. © 2016 Wiley Periodicals, Inc.

Key words: chemotherapy-induced nausea; chemotherapy-induced vomiting; clinical practice guideline; supportive care

INTRODUCTION

Children commonly experience chemotherapy-induced nausea and vomiting (CINV) despite administration of modern, guideline-consistent antiemetic agents. Children who experience CINV in previous chemotherapy blocks despite administration of prophylaxis (breakthrough CINV), which does not respond to the treatment or to changes in CINV prophylaxis are deemed to have refractory CINV. Achieving complete CINV control may be more difficult in these patients[1] and finding effective antiemetic interventions for them can be challenging. An evidence-based approach to optimizing CINV control in these patients is therefore essential.

The overall objective of this clinical practice guideline is to optimize breakthrough and refractory CINV control in children. This guideline applies to children aged 1 month to 18 years receiving chemotherapy. The target users of this guideline are all healthcare providers who care for these children. 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.

This guideline represents the fourth guideline in a series to address CINV in children. The three previously published guidelines address chemotherapy emetogenicity, prevention of acute CINV, and management of anticipatory CINV in children with cancer.[2–4] Complete versions of all four guidelines may be viewed at http://www.pogo.ca/healthcare/practiceguidelines/. Our recommendations are based on the assumption that children are receiving CINV prophylaxis that is consistent with the previously published guidelines.

METHODS

Guideline Panel and Development of Clinical Questions

Guideline panel members were chosen to represent interprofessional 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 (Table I) to be addressed by this guideline.

Systematic Literature Searches

In March 2015, computerized searches (Supplementary Table SI) were performed with the assistance of a library scientist to identify guidelines that could be endorsed for the treatment of breakthrough 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 (Table II) for endorsement assessment, the guideline panel proceeded to develop a *de novo* guideline. Systematic reviews of primary studies

Additional supporting information can be found in the supporting information tab for this article.

Abbreviations: CINV, chemotherapy-induced nausea and vomiting; CIV, chemotherapy-induced vomiting; EPS, extrapyramidal symptoms; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy

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TABLE I. Health Questions and Summary of Recommendations for the Treatment of Breakthrough Chemotherapy-Induced Nausea and Vomiting (CINV) and the Prevention of Refractory CINV in Children

Health questions and recommendations	Strength of recommendation and level of evidence[9,10]
Health question #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.	
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, we suggest 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, 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 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.	Weak recommendation Very low quality evidence
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.	
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, 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
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, we suggest 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, 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 • stimulation of Nei Gaun (P6) by means of acupressure or electroacupuncture.	Weak recommendation Very low quality evidence Weak recommendation Very low quality evidence

A recommendation summary table that includes the remarks for each recommendation is presented in Supplementary Table SVII.

evaluating interventions for the treatment of breakthrough CINV and the prevention of refractory CINV were conducted.

Evidence Identification and Synthesis

We searched for primary studies pertinent to the guideline topics (Supplementary Tables SII and SIII) 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 (Table II). Disagreements were resolved by a third reviewer. Evidence tables were compiled.

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[5] and prochlorperazine[6] were undertaken, and an existing systematic review of the safety of olanzapine[7] in children was considered by the panel. Primary studies

TABLE II. Study Inclusion Criteria for Three Systematic Reviews Undertaken

Guidelines
i. provided recommendations specifically for the management of breakthrough and/or refractory CINV; ii. were published in 2012 or more recently; iii. were based on a systematic review of the literature; and iv. were published in English.
Treatment of breakthrough CINV and prevention of CINV in patients who have experienced refractory CINV
i. were primary studies, other than single case reports; ii. were either fully published studies (no date restriction) or conference abstracts published in 2011 or more recently; iii. evaluated an intervention to treat breakthrough CINV or prevent CINV in refractory patients; iv. for prevention interventions: reported the proportion of patients experiencing complete control of CINV in refractory patients; and v. for treatment interventions: described the response to the first dose of the breakthrough treatment (ideally within the first 24 hr after administration) as a proportion of patients experiencing complete control or/and during the remainder of the phase in question (acute/delayed).
Safety of methotrimeprazine in children
i. published in English in a journal in full text or a letter to the editor reporting primary data; ii. included patients ≤18 years of age and either results were reported separately for patients ≤18 years of age or the mean or median age pf participants was ≤18 years; iii. described the adverse effects associated with the use of methotrimeprazine; and iv. the methotrimeprazine dose used was provided or, in the case of poisoning where the dose ingested was not able to be determined, a blood methotrimeprazine concentration was reported.

relating to the safety of methotrimeprazine in children were also searched (Supplementary Table SIII) 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 (Table II), and evidence summary tables were compiled as described above.

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 GRADE system.[8,9] In formulating recommendations, health benefits, adverse effects, and risks were explicitly considered.

External Review and Consultation Process

The draft guideline underwent a two-stage external review: first by international experts in 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 development guideline implementation tools.

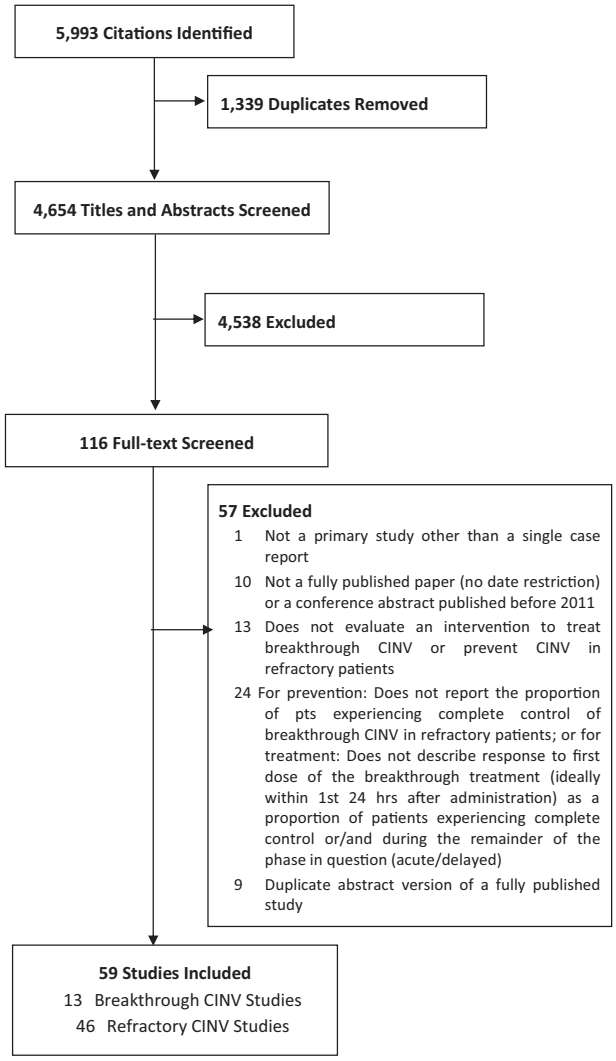

Fig. 1. Interventions to treat breakthrough chemotherapy-induced nausea and vomiting (CINV) or prevent CINV in refractory patients: Flowchart of literature identification process.

Procedure for Updating the Guideline

This guideline will be formally updated 5 years from publication or earlier should new, significant evidence become available.

RESULTS

A total of 4,654 references were identified from the database searches. Of these, 116 papers were reviewed in full text and 59 (breakthrough CINV: 13; refractory CINV: 46) satisfied the eligibility criteria (Fig. 1) and were included in the systematic review.

Health Question #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, which occurs during the acute or delayed phase despite CINV prophylaxis.

No studies were identified that described the treatment of breakthrough CINV exclusively in children. Thirteen studies in adults met criteria for inclusion (four randomized trials, two nonrandomized comparative studies, and seven prospective single-arm studies).

Evidence describing the treatment of breakthrough CINV in adults is summarized in Supplementary Table SIV. The guideline recommendations are summarized in Table I and Supplementary Table SVII. Studies evaluating ABH gel, 5-HT3 antagonists, and prochlorperazine were included in the evidence summary but were omitted from the recommendations due to poor systemic bioavailability,[10] inclusion as standard acute CINV prophylaxis[11] and safety concerns,[6] respectively.

Recommendation 1.1: For children receiving acute CINV prophylaxis recommended for minimally, low, or moderately emetogenic chemotherapy (MEC), clinicians should upgrade or escalate the acute CINV prophylaxis provided to that recommended for chemotherapy of the next higher level of emetogenic risk.

No specific evidence was identified that evaluated the escalation of CINV prophylaxis as treatment for breakthrough CINV in children. This recommendation is grounded in the evidence supporting the interventions recommended for acute CINV prophylaxis in children. [11]

This recommendation places a high value on the possible control of breakthrough CINV in the acute phase by providing antiemetic interventions (pharmacological and nonpharmacological) known to be effective in the setting of more emetogenic chemotherapy. It is a strong recommendation because the panel is certain that the benefits of acute CINV prophylaxis escalation outweigh the low risk of harms associated with these interventions.

Recommendation 1.2: For children receiving acute CINV prophylaxis recommended for highly emetogenic chemotherapy (HEC), we suggest that olanzapine be added to guideline-consistent CINV prophylaxis.

Adult patients. Two primary studies evaluated the use of olanzapine for the treatment of breakthrough CINV.[12,13] In a double-blind, randomized controlled trial, Navari et al. evaluated the efficacy of olanzapine versus metoclopramide for the treatment of breakthrough CINV in adult chemotherapy-naive patients receiving HEC and CINV prophylaxis with palonosetron, dexamethasone, and fosaprepitant.[13] At the onset of breakthrough CINV, patients were randomized to receive olanzapine (10 mg orally daily for 3 days) or metoclopramide (10 mg orally three times a day for 3 days). Dexamethasone was stopped when olanzapine or metoclopramide was initiated. The proportions of patients achieving complete control of breakthrough vomiting over the 72-hr observation period in the olanzapine and metoclopramide arms were 70% and 31% ($P < 0.01$), respectively. Similarly, a greater proportion of patients who received olanzapine (68%) achieved complete control of nausea compared to those patients receiving metoclopramide (23%, $P < 0.01$).

Chanthawong et al. described the efficacy of olanzapine for the treatment of breakthrough vomiting in adults receiving MEC or HEC.[12] In this prospective, open-label study, olanzapine (5 mg orally every 12 hours for two doses) was administered to patients experiencing breakthrough emesis despite prophylaxis with ondansetron, a corticosteroid, and metoclopramide. Complete control of breakthrough vomiting was experienced by 28 of 46 patients (61%) after olanzapine administration. Nausea was not evaluated.

No clinically significant adverse effects were reported in either study that evaluated olanzapine for the treatment of breakthrough CINV in adults. Dizziness, fatigue, and dyspepsia, described as mild and tolerable, were reported by Chanthawong et al.[12]

Pediatric patients. No pediatric studies of olanzapine for the treatment of breakthrough CINV were identified from the literature search. The guideline panel is aware of one recent paper, published after the March 2015 search end-date, which addresses the use of olanzapine in children. This multicenter, retrospective review described chemotherapy-induced vomiting (CIV) control and adverse effects in children receiving olanzapine.[14] In this cohort, 20 children received olanzapine for breakthrough CINV during 21 chemotherapy blocks. Complete CIV control was reported the day following the first olanzapine dose in 12 chemotherapy blocks (57%). Nausea control was not assessed.

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.[7] 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.

This recommendation is consistent with adult guidelines for the treatment of breakthrough CINV in adult cancer patients.[15,16] It places value on the high-quality evidence of the efficacy of olanzapine in adults receiving contemporary CINV prophylaxis. It is a weak recommendation because direct evidence of efficacy of olanzapine for prevention or treatment of CINV in children and of its safety in children receiving chemotherapy is limited or indirect. Furthermore, the optimal pediatric dose for this indication is uncertain. It may be reasonable to give olanzapine 0.1 mg/kg/dose (maximum 10 mg/dose) once daily by mouth. This dose is based on the results of the retrospective review[14] and uses the adult dose as the maximum dose. If CINV is not controlled and sedation does not occur or is not troublesome, the dose could potentially be increased to 0.14 mg/kg/dose (maximum 10 mg/dose). Olanzapine injection should not be administered for CINV control since it has not been evaluated for this indication. Olanzapine should be avoided in patients receiving CYP1A2 inducers (e.g., carbamazepine, rifampin) or inhibitors (e.g. ciprofloxacin, fluvoxamine) as olanzapine is primarily metabolized via this enzymatic pathway.[17]

Recommendation 1.3: For children receiving acute CINV prophylaxis recommended for HEC 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).

Addition of Methotrimeprazine

Adult patients. One prospective open-label study was identified that evaluated methotrimeprazine for the treatment of

breakthrough CINV in 32 patients. McCabe at al. evaluated the efficacy of a single 25 mg subcutaneous dose of methotrimeprazine for the treatment of breakthrough CINV occurring in the delayed phase in adult cancer patients receiving HEC.[18] The proportion of patients achieving complete control of breakthrough vomiting over the first 24 and 48 hr of methotrimeprazine administration was 88% and 94%, respectively. The proportion of patients achieving complete control of breakthrough nausea in 24 and 48 hr with administration of methotrimeprazine was 75% and 94%, respectively.

Drowsiness, dry mouth, and constipation are the most commonly reported adverse effects of methotrimeprazine in adult psychiatric patients[19]. 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 the previously described study.[18]

Pediatric patients. No evidence was identified that described the use of methotrimeprazine in children for the treatment of breakthrough CINV. Despite being licensed for use in children in Canada,[19] information regarding the use of methotrimeprazine in pediatric patients for any indication is limited. The pediatric dose recommended by the manufacturer is 0.25 mg/kg/day by mouth in two or three divided doses initially and increasing to a maximum of 40 mg/day in children 12 years of age or less.[19]

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 (Supplementary Table SV). No persistent adverse effects or fatalities were attributable to methotrimeprazine in these studies.

Addition of Metoclopramide

Adult patients. Two studies (a randomized controlled trial and a prospective observational study) were included. The randomized trial evaluating the efficacy of olanzapine versus metoclopramide for the treatment of breakthrough CINV in chemotherapy-naive adults receiving HEC has been described previously.[13] Musso et al. also evaluated the efficacy of metoclopramide (20 mg IV q6h or q12hr) versus a second dose of palonosetron (0.25 mg IV) in adults receiving either MEC or HEC.[20] Patients assigned to the metoclopramide arm received prophylaxis with ondansetron plus dexamethasone, while those in the palonosetron group received palonosetron plus dexamethasone. The proportion of patients achieving complete control of breakthrough CINV in the metoclopramide group was 22% versus 67% in the palonosetron group ($P = 0.039$).

Navari et al.[13] reported no grade 3 or 4 toxicities attributable to metoclopramide and Musso et al. stated that no serious adverse events observed in their study were attributable to antiemetic treatment.[20]

Pediatric patients. No evidence was identified that described the use of metoclopramide exclusively in pediatric patients for the treatment of breakthrough CINV. However, it is recommended for acute CINV prophylaxis in children as an alternate to dexamethasone.[11]

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%).[5] 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. Since Health Canada and the European Medicines Agency have recently issued warnings regarding the risk of EPS in young children receiving metoclopramide, the panel recommends that metoclopramide be avoided in children less than 1-year old.[21]

This recommendation is consistent with guidelines for adult cancer patients which recommend the use of metoclopramide for the treatment of breakthrough CINV in adults.[15,16] The panel recognizes that the evidence base for methotrimeprazine and metoclopramide consists of studies in adults that were not conducted in the context of currently recommended CINV prophylaxis. Despite these limitations and although direct evidence of efficacy of these agents for treatment of breakthrough CINV in children is not available, the guideline panel placed a high value on the possible benefit of these agents in the setting of breakthrough CINV. A lower value was placed on the potential for toxicity secondary to these agents because EPS are generally amenable to intervention and, although possibly distressing if not anticipated, are short-lived.

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.

Two studies were identified that described the prevention of refractory CINV in children: one prospective study evaluating the use of tropisetron[22] and a retrospective review evaluating the use of aprepitant.[23] Forty-one studies in adults met criteria for inclusion in this evidence base (five randomized trials, four nonrandomized prospective comparative studies, 31 prospective single arm studies, and one case series). Evidence describing the prevention of refractory CINV in children and adults is summarized in Supplementary Table SVI. Dexamethasone, tetrahydrocannabinol, levonantradol, Sancuso®, benzodiazepines, medroxyprogesterone, nabilone, and propofol were included in the evidence summary but were omitted from the recommendations. Similarly, placebo-controlled trials, dosage form comparison studies, or single-arm studies evaluating 5-HT3 antagonists other than palonosetron were omitted from the recommendations. This decision was taken for one or more of the following reasons: (1) the agent is currently recommended for acute CINV prophylaxis, (2) it is not available in a dosage form suitable for pediatric use, (3) outcome data have only been reported in an extremely small number of patients, (4) there is a lack efficacy data in the context of modern CINV prophylaxis, or (5) the agent is difficult to administer safely.

Recommendation 2.1: For children receiving acute CINV prophylaxis recommended for minimally, low, or MEC, clinicians should upgrade or escalate the acute CINV prophylaxis

provided to that recommended for chemotherapy of the next higher level of emetogenic risk.

No specific evidence was identified that evaluated the escalation of CINV prophylaxis as a preventative measure for refractory CINV in children. The panel felt that escalation of prophylaxis is a logical approach that is grounded in the evidence described previously in Recommendation 1.1.

This recommendation places a high value on the possible control of refractory CINV in the acute phase by provision of acute CINV prophylaxis (pharmacological and nonpharmacological) known to be effective in the setting of more emetogenic chemotherapy. It is a strong recommendation because the guideline panel is certain that the benefits of acute CINV prophylaxis escalation outweigh the low risk of harms associated with the interventions.

Recommendation 2.2: For children receiving acute CINV prophylaxis recommended for HEC, 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.

Switching from Ondansetron or Granisetron to Palonosetron

Adult patients. Two prospective open-label studies were identified. The first evaluated the efficacy and safety of a single IV dose of palonosetron in adults receiving chemotherapy with low emetogenic potential who had experienced refractory CINV.[24] Complete acute CINV control was achieved in 29 of 34 (85.3%) patients. A second study evaluated the efficacy of palonosetron in preventing refractory CINV in adults who had previously received CINV prophylaxis with either granisetron or ondansetron.[25] Complete CINV control rates in the acute and delayed phases of 77% and 81% were observed, respectively. The most commonly reported adverse effects reported by patients in this study were constipation and anxiety; no patient experienced severe toxicity.

Pediatric patients. No evidence was identified that described switching from ondansetron or granisetron to palonosetron in children for the prevention of refractory CINV. Palonosetron was recently approved for use in pediatric patients in the United States for prevention of acute CINV as a single dose of 20 μg/kg (max 1.5 mg) prior to chemotherapy.[26] The limited, peer-reviewed, published evidence to support its use in children has been summarized previously.[11]

This recommendation is consistent with adult guidelines related to palonosetron since it is considered the 5-HT3 antagonist of choice in adults receiving MEC.[15,27] It places a high value on the improved CINV control seen in adult cancer patients receiving palonosetron. It places less value on drug cost in the scenario where less expensive alternatives have been ineffective. It is a weak recommendation because direct evidence of the comparative efficacy of palonosetron for prevention of refractory CINV in children is not available. However, the available information (including approval by the U.S. Food and Drug Administration for the prevention of CINV in children) indicates that palonosetron can be used safely in pediatric cancer patients.

Switching from Ondansetron to Granisetron

Either ondansetron or granisetron is recommended for acute CINV prophylaxis in all children receiving chemotherapy of low, moderate, or high emetogenic risk.[11] There is no evidence to support use of one first generation 5-HT3 receptor antagonist over the other in children. However, ondansetron is primarily metabolized via the cytochrome P450 CYP 2D6 enzyme and studies in adults have shown that polymorphisms in this enzyme predispose patients to poor CINV control secondary to rapid ondansetron metabolism.[28]

Adult patients. A single study was identified that evaluated the efficacy of granisetron after CINV failure while receiving ondansetron in adults receiving HEC.[29] The authors reported complete CINV control (no vomiting and no or mild nausea) in 47% (9/19) of patients who received granisetron, while only 5% (1/21) of patients who continued to receive ondansetron experienced complete CINV control ($P = 0.005$).

Pediatric patients. No evidence was identified that described switching from ondansetron to granisetron in children for the prevention of refractory CINV.

If palonosetron is not available, it is suggested that granisetron be substituted for ondansetron in patients who experienced refractory CINV while receiving ondansetron. This recommendation is based on the potential for genetic variability in the enzymes responsible for metabolizing ondansetron. It places a high value on the improved CINV control seen in adult cancer patients receiving granisetron who have a genetic predisposition to a poor response to ondansetron at usual doses. It places less value on drug cost in the scenario where a less expensive alternative has been ineffective. It is a weak recommendation because direct evidence of using an alternative 5HT-3 antagonist for prevention of refractory CINV in children is not available.

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, we suggest that the addition of aprepitant to acute CINV prophylaxis be considered.

The use of aprepitant is currently recommended for acute CINV prophylaxis in children greater than or equal to 12 years of age receiving HEC, which is not known or suspected to interact with this agent[11] and recent evidence supports its use in children as young as 6 months.[30] Aprepitant is a CYP3A4 substrate and an inhibitor of CYP2C9/8 and CYP2C19. As a result, it may potentially interact with medications, including chemotherapy, metabolized via these pathways. The issues that must be considered when using aprepitant in pediatric patients have been summarized previously.[11] Interactions with chemotherapy that may lead to an increased risk of short- and long-term toxicity are of primary concern. However, direct evidence of these interactions is often unavailable and interpretation of the results of available studies that do evaluate aprepitant/fosaprepitant interactions with chemotherapy varies.

Adult patients. Six prospective, open-label studies were identified that evaluated the use of aprepitant in adults with refractory CINV receiving MEC or HEC. Since guidelines for CINV prophylaxis in adult cancer patients now recommend the use of aprepitant or its intravenous prodrug fosaprepitant as prophylaxis for HEC and for some MEC regimens,[15,16,27]

studies of aprepitant for breakthrough CINV will not be discussed.

Pediatric patients. One study was identified describing the use of aprepitant in children and adolescents with refractory CINV.[23] Bauters et al retrospectively evaluated the addition of aprepitant using the recommended adult dose (125 mg prior to chemotherapy on day one, followed by 80 mg once daily on days 2 and 3) to a 5-HT3 antagonist plus dexamethasone in 20 patients 8–16 years of age during 104 MEC or HEC blocks. Complete control of vomiting in the acute phase was achieved in 86% of chemotherapy blocks. The authors described aprepitant as well tolerated in combination with other antiemetics.

Additional experience with the use of aprepitant in adolescents is summarized in the pediatric acute CINV prophylaxis guideline.[11] Information regarding the use of aprepitant in younger children is growing and it is now approved in the United States for use in children 6 months of age and older.[30–35] Published experience with fosaprepitant in children is limited.[36]

This recommendation places a high value on improved CINV control when control is likely to be difficult to achieve and on the negative consequences of uncontrolled CINV. It is a weak recommendation since direct evidence of the efficacy of aprepitant in this context is lacking. 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.

Recommendation 2.4: 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 stimulation of Nei Guan (P6) by means of acupressure or electroacupuncture.

Inclusion of Successful Interventions Aimed at Breakthrough CINV in Acute CINV Prophylaxis

No specific evidence was identified that evaluated the efficacy of incorporating successful breakthrough CINV interventions from previous treatment blocks into the CINV prophylaxis provided for future chemotherapy blocks in children. Again, the panel felt that this is a logical approach and is another example of providing individualized care for patients. Olanzapine has been recommended for the treatment of breakthrough CINV in Recommendation 1.2. For children who cannot receive olanzapine, methotrimeprazine and metoclopramide have been recommended. In one study,[37] 62% of adults with refractory CINV achieved complete CINV control after administration of methotrimeprazine.

This recommendation places a high value on the potential for CINV control using interventions that are recommended for the treatment of breakthrough CINV and that were used successfully and without significant adverse effects in patients who previously experienced breakthrough CINV. It is a weak recommendation because the impact of the recommended action has not been evaluated.

TABLE III. Examples of Research Gaps Identified in the Domain of Treatment of Breakthrough Chemotherapy-Induced Nausea and Vomiting (CINV) and Prevention of Refractory CINV in Children

Domain	Issues
Breakthrough CINV	• Efficacy of CINV prophylaxis escalation • Optimal dose, efficacy, and safety of olanzapine and methotrimeprazine • Optimal dose, efficacy of metoclopramide, and risk factors for toxicity
Refractory CINV	• Optimal palonosetron dose in children receiving multiple day chemotherapy • Extent and clinical significance of interactions between aprepitant and chemotherapy

Addition of Acupressure or Acupuncture to Acute CINV Prophylaxis

Adult patients. One study evaluating the use of acupressure [38] and another evaluating the use of electroacupuncture [39] in adults with cancer were identified. Both were prospective, open-label studies of Nei Guan (P6) stimulation. It was not possible to determine if the CINV prophylaxis given in combination with acupressure was consistent with contemporary recommendations. However, 68% of patients had complete control of vomiting. Combining electroacupuncture with CINV prophylaxis consistent with contemporary recommendations resulted in complete vomiting control in 37% of adult patients.

Pediatric patients. No evidence was identified that described the use of acupressure or electroacupuncture in children for the prevention of refractory CINV.

This recommendation places a high value on the possibility that acupressure or acupuncture may increase control of CINV in patients who have experienced refractory CINV with a low potential for harm. It is a weak recommendation because there is a single study to support the use of each intervention in adults and there is no direct information regarding the efficacy or safety of acupressure/acupuncture in children with refractory CINV.

Research Gaps

The gaps in the evidence available to support recommendations for the control of breakthrough and refractory CINV in children are substantial. Examples are provided in Table III.

CONCLUSIONS

Recommendations for the treatment of breakthrough CINV and prevention of refractory CINV in children are summarized in Table I and in Supplementary Table SVII. These recommendations are based on a systematic review of the literature. However, there are many gaps in the available evidence. Optimization of 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.

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