Optimization of pediatric haematopoietic stem cell transplant outcomes through the application of pharmacokinetics and supportive care

Dupuis, Lee

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INTRODUCTION

Nausea and vomiting as a result of antineoplastic medication continue to be negative influences on the lives of children with cancer [1]. Although acute antineoplastic-induced vomiting (AIV) may improve over the course of treatment, antineoplastic-induced nausea (AIN) may actually become more problematic [2]. The use of evidence- or consensus-based guidelines for antiemetic selection has been shown to improve control of acute antineoplastic-induced nausea and vomiting (AINV) in adults [3]. The lack of a rigorously developed guideline for antiemetic selection in children receiving antineoplastic therapy has likely been an impediment to optimizing AINV control in children with cancer.

The purpose of this guideline is to provide health care providers who care for children receiving antineoplastic medication aged 1 month to 18 years with an approach to the prevention of acute AINV. Its scope is limited to the prevention of AINV in the acute phase (i.e., within 24 hours of administration of an antineoplastic agent) and does not include anticipatory, breakthrough or delayed phase AINV, or nausea and vomiting that is related to radiation therapy, disease, co-incident conditions or end-of-life care. In addition, this guideline is most applicable to children who are naïve to antineoplastic therapy.

This guideline represents the second of a series of guidelines to address the need for, and the selection of, antiemetic prophylaxis and intervention in children with cancer receiving antineoplastic medication. The first of this series has been published [4]. Full versions of both guidelines in this series are available on-line [5,6].

METHODS

Guideline Development Group

The Pediatric Oncology Group of Ontario (POGO) is a collaboration of the five pediatric oncology programs in Ontario, Canada. Members of the POGO AINV Guideline Development Panel were selected with a view to obtain inter-professional representation from within POGO and from recognized experts in pediatric AINV.

Key words: antiemetics; antineoplastic-induced nausea and vomiting; antineoplastics; chemotherapy-induced nausea and vomiting; nausea; vomiting

Source Guideline Selection

Using established methods [7,8], a source guideline was sought which addressed the health questions (Table I) that framed the development of this guideline. A comprehensive search of bibliographic databases and the gray literature was conducted in February 2010 with the assistance of a library scientist. Each guideline identified through the search was independently evaluated by three or four panel members using the AGREE instrument [7].

Additional Supporting Information may be found in the online version of this article.

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TABLE I. Summary of the Health Questions That Guided Development of the Guideline and the Recommendations Regarding Antiemetic Dosing for Prevention of Acute AINV in Children Receiving Antineoplastic Medication

<table>
<thead>
<tr>
<th>Health questions and recommendations</th>
<th>Strength of recommendation and level of evidence [10]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How is optimal control of acute AINV defined?</td>
<td></td>
</tr>
<tr>
<td>We recommend that optimal control of acute AINV be defined as no vomiting, no retching, no nausea, no use of antiemetic agents other than those given for AINV prevention and no nausea-related change in the child’s usual appetite and diet. This level of AINV 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.</td>
<td>Strong recommendation</td>
</tr>
<tr>
<td>2a. What pharmacological interventions provide optimal control of acute AINV in children receiving antineoplastic agents of high emetogenic risk?</td>
<td></td>
</tr>
<tr>
<td>We recommend that: Children ≥12 years old and receiving antineoplastic agents of high emetogenic risk which are not known or suspected to interact with aprepitant receive: ondansetron or granisetron+dexamethasone+aprepitant.</td>
<td>Strong recommendation</td>
</tr>
<tr>
<td>Children ≥12 years old and receiving antineoplastic agents of high emetogenic risk which are known or suspected to interact with aprepitant receive: ondansetron or granisetron+dexamethasone.</td>
<td>Moderate quality evidence</td>
</tr>
<tr>
<td>Children &lt;12 years old and receiving antineoplastic agents of high emetogenic risk receive: ondansetron or granisetron+dexamethasone.</td>
<td>Strong recommendation</td>
</tr>
<tr>
<td>2b. What pharmacological interventions provide optimal control of acute AINV in children receiving antineoplastic agents of moderate emetogenic risk?</td>
<td></td>
</tr>
<tr>
<td>We recommend that children receiving antineoplastic agents of moderate emetogenicity receive: ondansetron or granisetron+dexamethasone.</td>
<td>Strong recommendation</td>
</tr>
<tr>
<td>2c. What pharmacological interventions provide optimal control of acute AINV in children receiving antineoplastic agents of low emetogenic risk?</td>
<td></td>
</tr>
<tr>
<td>We recommend that children receiving antineoplastic agents of low emetogenicity receive: ondansetron or granisetron.</td>
<td>Strong recommendation</td>
</tr>
<tr>
<td>2d. What pharmacological interventions provide optimal control of acute AINV in children receiving antineoplastic agents of minimal emetogenic risk?</td>
<td></td>
</tr>
<tr>
<td>We recommend that children receiving antineoplastic agents of low emetogenicity receive: no routine prophylaxis.</td>
<td>Strong recommendation</td>
</tr>
<tr>
<td>3. What adjunctive non-pharmacological interventions provide control of acute AINV in children receiving antineoplastic agents of any emetogenic risk?</td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td>Weak recommendation</td>
</tr>
<tr>
<td>4. What is the role of aprepitant in children receiving antineoplastic therapy?</td>
<td></td>
</tr>
<tr>
<td>We recommend that the use of aprepitant be restricted to children 12 years of age and older who are about to receive highly emetogenic antineoplastic therapy which is not known or suspected to interact with aprepitant. There is no evidence to support the safe and effective use of apreptitant in younger children.</td>
<td>Strong recommendation</td>
</tr>
<tr>
<td>5. What pharmacological interventions provide optimal control of acute AINV in children receiving highly or moderately emetogenic antineoplastic agents in whom corticosteroids are contra-indicated?</td>
<td></td>
</tr>
<tr>
<td>We suggest that children receiving highly emetogenic antineoplastic therapy who cannot receive corticosteroids receive: ondansetron or granisetron+chlorpromazine or nabilone.</td>
<td>Weak recommendation</td>
</tr>
<tr>
<td>We suggest that children receiving moderately emetogenic antineoplastic therapy who cannot receive corticosteroids receive: ondansetron or granisetron+chlorpromazine or metoclopramide or nabilone.</td>
<td>Weak recommendation</td>
</tr>
<tr>
<td>6. What doses of antiemetic agents are known to be effective in children receiving antineoplastic agents?</td>
<td></td>
</tr>
<tr>
<td>We recommend the following aprepitant dose for children 12 years of age and older: Day 1: 125mg PO×1; Days 2 and 3: 80mg PO once daily. We recommend the following chlorpromazine dose: 0.5mg/kg/dose IV q6h. We suggest the following dexamethasone for children receiving highly emetogenic antineoplastic therapy: 6mg/m²/dose IV/PO q6h.</td>
<td>Strong recommendation</td>
</tr>
</tbody>
</table>

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### TABLE I. (Continued)

<table>
<thead>
<tr>
<th>Health questions and recommendations</th>
<th>Strength of recommendation and level of evidence [10]</th>
</tr>
</thead>
<tbody>
<tr>
<td>If given concurrently with aprepitant, reduce dexamethasone dose by half. We recommend the following dexamethasone for children receiving moderately emetogenic antineoplastic therapy:</td>
<td></td>
</tr>
<tr>
<td>&lt;0.6m²: 2mg/dose IV/PO q12h</td>
<td></td>
</tr>
<tr>
<td>≥0.6m²: 4mg/dose IV/PO q12h.</td>
<td></td>
</tr>
<tr>
<td>If given concurrently with aprepitant, reduce dexamethasone dose by half. We recommend the following IV granisetron dose for children receiving highly emetogenic antineoplastic therapy: 40mcg/kg/dose IV as a single daily dose.</td>
<td></td>
</tr>
<tr>
<td>We recommend the following IV granisetron dose for children receiving moderately emetogenic antineoplastic therapy: 40mcg/kg/dose IV as a single daily dose.</td>
<td></td>
</tr>
<tr>
<td>We suggest the following oral granisetron dose for children receiving moderately emetogenic antineoplastic therapy: 40mcg/kg/dose PO q12h.</td>
<td></td>
</tr>
<tr>
<td>We recommend the following IV granisetron dose for children receiving antineoplastic therapy of low emetogenicity: 40mcg/kg/dose IV as a single daily dose.</td>
<td></td>
</tr>
<tr>
<td>We suggest the following oral granisetron dose for children receiving antineoplastic therapy of low emetogenicity: 40mcg/kg/dose PO q12h.</td>
<td></td>
</tr>
<tr>
<td>We recommend the following metoclopramide dose for children receiving moderately emetogenic antineoplastic therapy: 1mg/kg/dose IV pre-therapy ×1 then 0.0375mg/kg/dose PO q6h.</td>
<td></td>
</tr>
<tr>
<td>Give diphenhydramine or benztropine concurrently.</td>
<td></td>
</tr>
<tr>
<td>We suggest the following nabilone dose:</td>
<td></td>
</tr>
<tr>
<td>&lt;18kg: 0.5mg/dose PO twice daily</td>
<td></td>
</tr>
<tr>
<td>18–30kg: 1mg/dose PO twice daily</td>
<td></td>
</tr>
<tr>
<td>&gt;30kg: 1mg/dose PO three times daily.</td>
<td></td>
</tr>
<tr>
<td>Maximum: 0.06mg/kg/day.</td>
<td></td>
</tr>
<tr>
<td>We recommend the following ondansetron dose for children receiving highly emetogenic antineoplastic therapy: 5mg/m²/dose (0.15mg/kg/dose) IV/PO pre-therapy ×1 and then q8h.</td>
<td></td>
</tr>
<tr>
<td>We recommend the following ondansetron dose for children receiving moderately emetogenic antineoplastic therapy: 5mg/m²/dose (0.15mg/kg/dose; maximum 8mg/dose) IV/PO pre-therapy ×1 and then q12h.</td>
<td></td>
</tr>
<tr>
<td>We recommend the following ondansetron dose for children receiving therapy of low emetogenicity: 10mg/m²/dose (0.3mg/kg/dose; maximum 16mg/dose IV) IV/PO pre-therapy ×1.</td>
<td></td>
</tr>
</tbody>
</table>

### Pediatric Evidence Identification and Synthesis

None of the guidelines identified specifically addressed antiemetic use for the prevention of acute AINV in children. Therefore, a systematic review of primary pediatric oncology studies addressing this topic was conducted through November 1, 2011 with the assistance of a library scientist. Panel members also reviewed their personal files for papers that met inclusion criteria. The search strategy is available in the on-line version of the guideline [6]. Studies were included if they were published in full text in English or French; reported pediatric data separately; provided sufficient detail to allow assessment of the emetogenicity of the antineoplastic therapy administered using the POGO classification guideline or provided an assessment by the study’s author(s); provided an explicit or implicit definition of complete acute AINV response; and reported the complete acute AINV response rate as a proportion or percentage.

Citations were divided among panel members for screening for inclusion/exclusion. Full-text screening was performed for citations identified as potentially relevant. Evidence summary tables were compiled and reviewed by two panel members before consideration by the panel.

A meta-analysis was undertaken to evaluate the contribution of each antiemetic agent or antiemetic regimen to complete AINV control. Because of the paucity of randomized controlled trials (RCTs), all outcomes were described as proportions; for example, the proportion of patients with complete AINV control among a particular group. Each study was weighted by the inverse variance. Given the anticipation of heterogeneity between studies, a random effects model [9] was used for all analyses. Meta-analysis was performed using Review Manager (RevMan Version 5.1.0, The Cochrane Collaboration, Oxford, England). Sub-groups were compared by evaluating heterogeneity across sub-group results.

Therapeutic efficacy and safety were the primary determinants of recommendations made by the panel regarding antiemetic choice. In the event of contradictory information regarding therapeutic efficacy, panel members took a conservative approach; that is, the more aggressive, comprehensive antiemetic prophylaxis would be recommended since this approach would be more likely to lead to complete AINV control.

Emetogenicity was defined as per the first POGO AINV guideline [4,5]. That is, high, moderate, low, and minimal emetogenicity were defined as a >90%, 30 to <90%, 10 to <30%, and <10% chance of causing emesis when antiemetic prophylaxis was not provided. A listing of the emetogenicity of antineoplastic agents in children is provided in Supplementary Tables I and II.
The authors of several studies categorized the emetogenicity of the antineoplastic regimens they studied as high or moderate without providing sufficient detail to determine the emetic risk as per the first POGO AINV guideline [4,5]. In making recommendations, less weight was placed on the results of these studies than those where the emetogenicity of the antineoplastic regimens studied was able to be verified against the POGO classification.

Authors of some studies described the AINV experienced by children receiving antineoplastic therapy of varied emetogenicity and reported the AINV control results for the group as a whole. When the results of these studies were reported, a conservative approach was used: the study results were reported in the lowest emetogenic risk category included. Authors of other studies described AINV control in children receiving multiple day antineoplastic regimens where the emetogenicity varied between treatment days and where AINV control was reported for the entire acute phase. In these, the study results were reported according to the individual agents of highest emetogenicity given during the antineoplastic block.

Decisions were taken through panel discussions. Differences in interpretation 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 [10] by one author (L.L.D.) and confirmed through discussion by the remaining panel members.

**External Review and Consultation Process**

The draft guideline underwent an extensive two-stage external review: first by international experts in adult and pediatric AINV and then by stakeholders from the Ontario pediatric oncology community. Seven content experts provided a review; their comments were discussed in detail by the panel and a decision on each point was taken by consensus. Thirty stakeholder responses were received. No changes were made to the recommendations based on the stakeholders’ comments. However, wording of the guideline was clarified and an appendix describing recommended adult antiemetic doses was added.

**RESULTS**

**Source Guideline Identification**

The guideline search yielded 60 citations that were screened for inclusion. Of these, 13 guidelines were assessed using the AGREE instrument. Two guidelines were selected for adaptation; these were developed by The American Society of Clinical Oncology (ASCO) [11,12] and by Tipton et al. [13]. When it became available, the 2011 update to the ASCO guideline [12] was compared to the previous version. Since the 2011 recommendations did not differ substantially from those provided in the 2006 version with respect to the health questions of interest, the 2011 update was cited as the source guideline.

The ASCO guideline [12] was the primary framework used for the development of guidelines for AINV prevention in pediatric cancer patients for pharmacological therapies. Although this guideline provides a general recommendation for AINV prophylaxis in children, its focus is on antiemetic use for adult cancer patients and it is in this capacity that the guideline is referenced as a source document. Tipton et al. [13] was used as the framework for non-pharmacological interventions.

**Primary Pediatric Literature Review**

One thousand six hundred sixty references were identified resulting in 72 papers that met eligibility criteria (Fig. 1). The recommendations of the POGO Guideline for the Prevention of Acute AINV in Children receiving Antineoplastic Medication are summarized in Figure 2 and Table I. The evidence tables supporting these recommendations are available at: http://www.pogo.ca/healthcare/practiceguidelines/acuteainvguideline/. The rationale for the recommendations is summarized below.

**How Is Optimal Control of Acute AINV Defined?**

The source guidelines [12,13] did not explicitly address this question and no pertinent evidence was identified. The recommendation reflects the consensus of the guideline panel.

**What Pharmacological Interventions Provide Optimal Control of Acute AINV in Children Receiving Antineoplastic Medications of High Emetic Risk?**

The reported rates of complete AINV control in children receiving highly emetogenic antineoplastic agents (HEC) were consistently low regardless of whether the emetogenicity of the antineoplastic regimens included in studies was defined as per the POGO guideline (43%; 95% CI: 29, 56) or by the investigators (47%; 95% CI: 22, 72).

5-HT3 antagonist, corticosteroid plus aprepitant. The source guideline [12] recommends administration of a 5-HT3 antagonist, dexamethasone plus aprepitant to adults receiving HEC. Minimal pediatric data regarding aprepitant has been published; nevertheless, anecdotally, many pediatric clinicians have adopted it for routine use. Aprepitant is recommended for the age group where there is published information regarding safety (12 years of age and older) and for patients who are not receiving medications which may result in clinically important drug interactions with aprepitant. A subsequent health question specifically addresses the use of aprepitant in children.

5-HT3 antagonist plus corticosteroid. Evaluations of the efficacy of a 5-HT3 antagonist plus dexamethasone in children receiving HEC are limited to four studies [14–17]. The emetogenicity of the antineoplastic agents administered in all four studies was able to be determined using the POGO classification guideline. Synthesis of these studies observed a complete AINV control rate of 50% (95% CI: 43%, 57%). Nausea assessment was included in the definition of complete control in two of these studies [15,16]. The observed complete AINV control rate in these studies was similar (48%; 95% CI: 41%, 56%).

In the only pediatric RCT, the use of both ondansetron plus dexamethasone resulted in a higher rate of complete vomiting control than did the use of ondansetron alone (61% vs. 23%; no P-value provided) [14]. The recommendation for the use of a 5-HT3 antagonist plus a corticosteroid for prevention of acute AINV in children receiving HEC is also supported by a meta-analysis which observed that the addition of a corticosteroid to a 5-HT3 antagonist resulted in a relative risk (RR) of complete control of vomiting of 2.03 (95% CI: 1.35, 3.04) [18].

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What Pharmacological Interventions Provide Optimal Control of Acute AINV in Children Receiving Antineoplastic Medications of Moderate Emetic Risk?

The source guideline [12] recommends palonosetron plus dexamethasone for adults about to receive MEC. Synthesis of all studies evaluating antiemetic efficacy in children receiving moderately emetogenic antineoplastic therapy (MEC) observed a complete AINV control rate of 45% (95% CI: 31%, 58%). Until more evidence is available regarding the efficacy and safety of palonosetron in children, it is not possible to include it in recommendations for acute AINV control in children.

5-HT3 antagonist plus corticosteroid. No studies which defined the emetogenicity of the antineoplastic agents administered using the POGO guideline or which defined complete AINV control as the control of both vomiting and nausea were identified. White et al. [19] evaluated the efficacy of dexamethasone plus either oral or IV ondansetron in an RCT in 428 children about to receive what the authors described as MEC or HEC. On the first day of the antineoplastic block, complete control of vomiting and retching was achieved in 78–81% of children whereas control of nausea was achieved in 70–73%. These results may underestimate the degree of AINV control that may be possible in children receiving MEC since some received HEC. Nevertheless, this relatively large study

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**Fig. 1. Literature Search for Pediatric Studies Results Flowchart.** Details of the literature search are available on-line at http://www.pogo.ca/healthcare/practiceguidelines/.
confirms the source guideline’s recommendation of a 5-HT3 antagonist plus dexamethasone for patients about to receive MEC. A single study evaluated palonosetron in 53 children (mean age 6.6 years) over 138 MEC blocks observed complete acute AINV control (no emesis and no rescue therapy) in 84.1% [20].

**What Pharmacological Interventions Provide Optimal Control of Acute AINV in Children Receiving Antineoplastic Medications of Low Emetic Risk?**

The source guideline recommends dexamethasone alone for patients about to receive antineoplastic agents of low emetic risk. There were no pediatric studies identified which addressed the efficacy of dexamethasone in this population. In the complete absence of supporting evidence for its application to pediatrics, the panel did not adopt the source guideline’s recommendation.

Synthesis of all studies that evaluated an antiemetic intervention in children receiving antineoplastic agents of low emetic risk observed an overall complete control rate of 75% (95% CI: 66%, 85%).

**5-HT3 antagonist alone.** Synthesis of the studies which evaluated the AINV control provided by 5-HT3 antagonists alone observed a rate of complete AINV control of 74% (95% CI: 62%, 87%). All identified studies evaluated the use of 5-HT3 antagonists alone in the setting of antineoplastic agents of low emetogenicity as defined by the POGO guideline and included nausea control in their definition of complete AINV control. Three studies were RCTs [21–23]. Reported complete control rates ranged from 50% to 91%.

**What Pharmacological Interventions Provide Control of Acute AINV in Children Receiving Antineoplastic Medications of Minimal Emetic Risk?**

No pediatric studies which evaluated AINV control in children receiving antineoplastic agents of minimal emetic risk without antiemetic prophylaxis were identified. The recommendation of the...
Antineoplastic-Induced Nausea and Vomiting in Children

Given the scarcity of evidence-based options, the panel recommended that nabilone or chlorpromazine be administered together with ondansetron or granisetron to children receiving HEC in whom corticosteroids are contra-indicated. Metoclopramide is a third option for children receiving MEC.

Chlorpromazine. Published experience with chlorpromazine for AINV prophylaxis is limited [26,27] yet general pediatric experience with it is extensive. The antiemetic activity of chlorpromazine has not been evaluated in combination with a 5-HT3 antagonist. Its use strictly in the in-patient setting seems prudent based on its sedating and hypotensive properties. The concurrent use of diphenhydramine or benzotropine to prevent chlorpromazine-induced extrapyramidal effects may be considered.

Nabilone. A meta-analysis of experience with cannabinoids for the prevention of AINV concluded that cannabinoids were better at controlling antineoplastic-induced vomiting (RR: 1.28, 95% CI: 1.08–1.51) and antineoplastic-induced nausea (RR: 1.38; 95% CI: 1.18–1.62) than prochlorperazine, metoclopramide, domperidone, or haloperidol [28]. A randomized cross-over trial of the antiemetic activity of nabilone compared the antiemetic activities of nabilone and prochlorperazine [29]. A higher proportion of children experienced an improvement in emesis (21 of 30 vs. 9 of 30; \(P = 0.003\)) during the nabilone phase of the study and more patients preferred nabilone to prochlorperazine (20 of 30 vs. 5 of 30; \(P = 0.015\)). The most common adverse effects experienced by children in the nabilone phase were dizziness and drowsiness; dose reduction improved these symptoms without reducing the therapeutic benefit.

Metoclopramide. A single RCT compared the AINV control provided by metoclopramide plus diphenhydramine versus ondansetron in children receiving chemotherapy of low to high emetogenicity [21]. Metoclopramide administration led to a higher AINV complete control rate in children receiving antineoplastic therapy of low to moderate emetogenic potential (74%) than of high emetic potential (11%).

What Doses of Antiemetic Agents Are Known to Be Effective in Children Receiving Antineoplastic Medications?

Aprepitant. In all but two publications to date, children were given the recommended adult dose of aprepitant; that is, 125 mg on Day 1 followed by 80 mg on Days 2 and 3 [17,24,30–32]. Choi et al. [25] gave this dose to children who weighed greater than 20 kg and a lower dose (80 mg/day for 3 days) to children who weighed less than 20 kg. The extent of AINV control afforded by each dosing scheme was not provided. Coppola et al. [33] reviewed the use of aprepitant in 33 children less than 18 years old. Children weighing less than 40 kg were most often given aprepitant 80 mg on Day 1 followed by 80 mg on Days 2 and 3 [17,24,30–32]. Choi et al. [25] gave this dose to children who weighed greater than 20 kg and a lower dose (80 mg/day for 3 days) to children who weighed less than 20 kg. The extent of AINV control afforded by each dosing scheme was not provided. Coppola et al. [33] reviewed the use of aprepitant in 33 children less than 18 years old. Children weighing less than 40 kg were most often given aprepitant 80 mg on Day 1 and then 40 mg per day on Days 2 and 3. Details regarding the antineoplastic therapy and other antiemetic agents given concurrently were not provided.

The pharmacokinetic disposition of aprepitant in adolescents has been shown to be similar to that observed in adults [24]. It is therefore reasonable to administer the adult dose to adolescents. However, the pharmacokinetic disposition of aprepitant in infants and pre-adolescent children is unknown and no dose-finding studies have been conducted in this age group.

Chlorpromazine. The use of chlorpromazine for AINV control in children has been described in six studies, five of which were

source guidelines [11,12] to give no routine antiemetic prophylaxis was therefore adopted.

What Adjunctive Non-Pharmacological Interventions Provide Control of Acute AINV in Children Receiving Antineoplastic Medications of Any Emetic Risk?

No pediatric evidence to support the source guideline’s recommendation was identified. In the opinion of the panel, the measures included in the source guideline’s recommendation are unlikely to result in undesirable effects or adversely affect quality of life and may convey benefit. The recommendations of the source guideline were therefore adopted by the guideline panel despite the lack of pediatric supporting information.

What Is the Role of Aprepitant in Children Receiving Antineoplastic Medication?

Published pediatric experience with aprepitant is exceedingly sparse and of poor quality. A single prospective trial has been published to date but its primary aim was to describe the pharmacokinetics of aprepitant [24]. The available published pediatric descriptions of aprepitant use in children are also insufficient to judge its safety in this age group. Gore et al. [24] observed a higher incidence of febrile neutropenia in children receiving aprepitant compared to controls (25% vs. 11.1%). Choi et al. [25] describe hyperglycemia in 2 of 32 children included in a retrospective review.

As a cytochrome P-450 isoenzyme 3A4 (CYP3A4) substrate and inhibitor and an inhibitor of CYP2C9/8 and CYP2C19, aprepitant has the potential for increasing the dose intensity of other CYP3A4 substrates given concurrently. Potential interactions between aprepitant and antineoplastic agents are of utmost concern due to their potential impact on toxicity and long-term outcomes. Supplementary Tables III and IV list the antineoplastic agents classified as highly emetogenic when given alone or with other antineoplastic agents which rely on CYP3A4 for their metabolism or bioactivation or which are known to interact with aprepitant. The concurrent use of aprepitant with these agents may lead to increased toxicity or, in some cases, decreased therapeutic effect.

To balance the desire to better control AINV against the large gaps in our knowledge about how best to dose and administer aprepitant to children, the panel recommends that the routine use of aprepitant be reserved for patients in the age group for which there is information to support a dosing guideline (12 years of age and older) and who are about to receive highly emetogenic antineoplastic therapy whose dose intensity will not be altered by concurrent administration with aprepitant.

What Pharmacological Interventions Provide Optimal Control of Acute AINV in Children Receiving Highly or Moderately Emetogenic Antineoplastic Medication in Whom Corticosteroids Are Contra-Indicated?

The source guidelines [12,13] did not address this question. It is clear that prophylaxis with a 5-HT3 antagonist alone leads to poor AINV control in patients receiving MEC and HEC. Synthesis of the three studies which evaluated alternative antiemetic agents (chlorpromazine, metoclopramide) in children receiving HEC observed a complete AINV control rate of 9% (95% CI: 0, 20).
blinded RCTs [26,27,34–37]. Doses ranged from 0.3 to 1 mg/kg every 3–6 hours; Hahnen and Quintana [34] initiated their investigation using a dose of 0.5 mg/kg and later reduced it to 0.3 mg/kg due to excessive sedation. Since higher doses within this range were most often evaluated, the guideline development panel recommended a starting chlorpromazine dose of 0.5 mg/kg/dose IV given every 6 hours with consideration of a higher dose if AINV is not controlled and sedation is not a concern.

**Dexamethasone**

**Highly emetogenic antineoplastic therapy.** Five studies were identified in which antineoplastic therapy was assessed as HEC using the POGO guideline or as stated by the investigators. Four of these were RCTs [14,17,26,38]; one was a prospective descriptive study [16]. Of the RCTs, three were conducted exclusively in children [14,26,38]. Doses ranged from approximately 6 to 24 mg/m²/day IV. In the largest of these studies, two dexamethasone dosing regimens (24 mg/m²/day: 8 mg/m²/dose given IV pre-therapy x 1 and then 16 mg/m²/day IV either divided q6h or divided into two doses given q4h) were given. However, the results were presented in aggregate [14]. These studies did not evaluate AINV control using common antiemetic backbones so comparison of the performance of the dexamethasone doses used is not possible. The fourth RCT involved too few children to permit evaluation of the outcome in this subset [17].

The recommendation for dexamethasone dosing is based on the most robust, published evidence [14,26,38] in children receiving HEC. Because assignment of a maximum dose would be arbitrary, no maximum dexamethasone dose is recommended in this guideline. The dexamethasone dose should be halved in patients receiving aprepitant concurrently.

**Moderately emetogenic antineoplastic therapy.** Three studies were identified in which chemotherapy was classified as MEC using the POGO guideline [5] or as deemed by the investigators [19,34,39]. All were randomized comparisons of varying antiemetic regimens, in which at least one arm included dexamethasone. A single RCT evaluated AINV control provided by dexamethasone plus either oral or IV ondansetron in children receiving MEC or HEC [19]. Dexamethasone was given by mouth in a dose based on body surface area (≤0.6 m²: 2 mg BID; >0.6 m²: 4 mg BID). This dosing regimen is approximately equivalent to 5–20 mg/m²/day depending on the child’s size. The complete antiemetic-induced vomiting control rate observed in this study was approximately 80%. No other study has evaluated the combination of dexamethasone plus a 5-HT3 antagonist in children receiving MEC. The other two studies identified compared dexamethasone doses ranging from 6 to 10 mg/m²/day combined with either chlorpromazine or metoclopramide [19,34].

The panel’s recommendation regarding the dexamethasone dose to be given to children receiving MEC stems from the observations of White et al. [19]. Given the highly variable dexamethasone clearance in children [40] and the lack of specific information regarding bioavailability of dexamethasone in children, it is reasonable to recommend the same dose IV in cases where the oral route of administration is not appropriate.

**Granisetron**

**Highly emetogenic antineoplastic therapy.** One randomized crossover trial compared two granisetron doses (20 or 40 mcg/kg/dose once daily) plus dexamethasone in 13 children receiving HEC [41]. All patients achieved complete AINV control regardless of the granisetron dose administered. No patient required rescue antiemetic agents.

In an open prospective study, Miyajima et al. gave granisetron as a single daily dose of 40 mcg/kg and observed complete AINV control in approximately 60% of children receiving HEC. Although the study protocol allowed for the administration of a second granisetron dose in patients in whom AINV control was not ideal, no patient required a second granisetron dose. This level of control is similar to that reported in children receiving HEC and single agent 5-HT3 antagonists for AINV prevention as reported in recommendation 2; that is, 66% (95% CI: 60, 72).

Granisetron 40 mcg/kg/day IV as a single daily dose is recommended for children receiving HEC. The very small number of patients included in the dose comparison trial by Komada et al. [41] limits the confidence that giving a granisetron dose of 20 mcg/kg/dose will achieve the same degree of AINV control as seen following a larger dose. A maximum granisetron dose is not recommended since neither of the identified studies capped the dose.

**Moderately emetogenic antineoplastic therapy.** IV Granisetron: Dose comparison studies in small numbers of children receiving MEC indicate no difference in rates of complete AINV control offered by granisetron 20 mcg/kg/dose or 40 mcg/kg/dose [34,41]. Fujimoto et al. [42] made similar observations in children receiving antineoplastic therapy of unknown emetogenicity. However, Tsuchida et al. [43] observed a significant difference in the complete AINV control rates achieved in children receiving antineoplastic therapy of unknown emetogenicity depending on the granisetron dose administered (20 mcg/kg/dose vs. 40 mcg/kg/dose). Furthermore, the findings of improved control with repeated doses of granisetron 20 mcg/kg raise questions about the reliability of gaining complete AINV control with single granisetron doses of 20 mcg/kg [34,44]. For these reasons, the panel recommends that granisetron 40 mcg/kg be given as a single daily dose to children receiving MEC. No maximum dose is recommended since all but one study had no dose limit.

Oral Granisetron: Based on the findings of Mabro et al. [45], the panel recommends that children receiving MEC receive granisetron 40 mcg/kg/dose every 12 hours by mouth. No maximum dose is recommended.

**Antineoplastic therapy of low emetogenic potential.** Two randomized trials met the inclusion criteria [23,46]. Both administered granisetron in doses of 40 mcg/kg IV as a single daily dose prior to antineoplastic therapy of low to high emetogenicity. In one study, the maximum granisetron dose was 3 mg regardless of body weight [46].

**Metoclopramide.** Four randomized trials that evaluated the use of metoclopramide to prevent AINV in children were included and support the recommended metoclopramide dose [21,26,39,47]. The recommended dose was associated with a complete rate of vomiting control of 74% (17/23) [21]. Concurrent administration of diphenhydramine is recommended due to the high likelihood of dystonic reactions.

**Nabilone.** A single randomized trial met the criteria for inclusion in the evidence summary. It describes AINV control in 30 children receiving antineoplastic therapy [29]. The panel based the recommended nabilone dose on this trial. A maximum dose is recommended due to increased toxicity observed above this threshold [48].

**Ondansetron**

**Highly emetogenic antineoplastic therapy.** Three randomized trials evaluated acute AINV control in children receiving HEC.
Antineoplastic-Induced Nausea and Vomiting in Children

TABLE II. Identified Research Gaps in the Domain of Prevention of Antineoplastic-Induced Nausea and Vomiting in Children

<table>
<thead>
<tr>
<th>Domain</th>
<th>Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes</td>
<td>Impact on each component of AINV control (vomiting, retching, nausea, appetite and use of breakthrough antiemetic agents) on quality of life</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Highly emetogenic antineoplastic therapy: 5-HT3 antagonist plus a corticosteroid</td>
</tr>
<tr>
<td></td>
<td>5-HT3 antagonist, a corticosteroid plus aprepitant</td>
</tr>
<tr>
<td></td>
<td>Moderately emetogenic antineoplastic therapy: 5-HT3 antagonist plus a corticosteroid</td>
</tr>
<tr>
<td></td>
<td>5-HT3 antagonist plus aprepitant/fosaprepitant</td>
</tr>
<tr>
<td></td>
<td>Adjunctive antiemetic agent for use in children who cannot receive corticosteroid</td>
</tr>
<tr>
<td></td>
<td>Novel antiemetic agents: aprepitant/fosaprepitant, casopitant, rolapitant, palonosetron, diphenhydramine-lorazepam-dexamethasone, ginger, metopimazine, olanzapine</td>
</tr>
<tr>
<td></td>
<td>Novel antiemetic interventions: acupressure, guided imagery, music therapy, progressive muscle relaxation, psycho-educational support, virtual reality, and food composition and presentation</td>
</tr>
<tr>
<td></td>
<td>Role of genetics on risk of AINV and antiemetic efficacy</td>
</tr>
<tr>
<td>Dosage optimization</td>
<td>Dose-finding studies including determination of maximum doses: dexamethasone, oral granisetron</td>
</tr>
<tr>
<td></td>
<td>Dose frequency (single vs. multiple daily doses): dexamethasone, ondansetron</td>
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<tr>
<td></td>
<td>Dose strategies in obese children</td>
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<tr>
<td>Safety</td>
<td>Interaction between aprepitant/fosaprepitant and antineoplastic agents</td>
</tr>
<tr>
<td></td>
<td>Short and long term adverse effects of corticosteroid use such as mood changes, sleep disturbance, fatigue and osteopenia</td>
</tr>
<tr>
<td>Product formulation</td>
<td>Oral liquid aprepitant, granisetron, nabilone, palonosetron</td>
</tr>
</tbody>
</table>

The number of children involved in one of these trials is too small to allow interpretation [17]. The remaining studies which assessed AINV control after ondansetron administration were descriptive in nature [16,50–54]. The recommendation was based on the findings of RCTs and supported by descriptive studies. The ondansetron dose was capped at 8 mg q8h in a single open, non-comparative, prospective study of children receiving HEC [55]. The small number of children evaluated in this study and the low complete control rate observed did not support the inclusion of a maximum ondansetron dose as a recommendation.

**Moderately emetogenic antineoplastic therapy.** Five randomized trials meeting inclusion criteria administered ondansetron to children receiving MEC [19,39,56–58]. The findings of these and other descriptive studies [52,55,59] support the recommendation. The maximum single dose of 8 mg is based on the findings of good AINV control in two RCTs [39,56] and one prospective study [55] where the dose limit was 8 mg.

**Antineoplastic therapy of low emetogenic potential.** Two studies met inclusion criteria: one RCT [22] and another descriptive study [16]. Both describe outcomes in a very small number of patients. Neither study administered a maximum ondansetron dose; however, the panel recommends a maximum single daily IV ondansetron dose of 16 mg due to the potential for QT interval prolongation with higher doses [60]. Based on the excellent bioavailability of ondansetron and its demonstrated efficacy in children receiving HEC or MEC when given by mouth, the guideline development panel furthermore included the oral route in the recommendation despite the absence of specific evidence to support its efficacy in children receiving antineoplastic of low emetogenic potential.

**RESEARCH GAPS**

The number of significant gaps in the published evidence regarding interventions which may provide optimal AINV control to children is extensive. Examples are presented in Table II.

**CONCLUSIONS**

Recommendations for the prevention of AINV in children receiving antineoplastic agents are summarized in Table I and Figure 2. Readers are encouraged to adapt these recommendations to their local context. The development of an evidence-based approach to antiemetic selection in children receiving antineoplastic therapy is likely to improve AINV control. However, there are many gaps in our knowledge. AINV control in children is not likely to be fully optimized until specific information regarding the pediatric use of antiemetic agents known to be critical to AINV control in adults is generated.

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