Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update

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ABSTRACT

Purpose
To update the American Society of Clinical Oncology (ASCO) guideline for antiemetics in oncology.

Methods
A systematic review of the medical literature was completed to inform this update. MEDLINE, the Cochrane Collaboration Library, and meeting materials from ASCO and the Multinational Association for Supportive Care in Cancer were all searched. Primary outcomes of interest were complete response and rates of any vomiting or nausea.

Results
Thirty-seven trials met prespecified inclusion and exclusion criteria for this systematic review. Two systematic reviews from the Cochrane Collaboration were identified; one surveyed the pediatric literature. The other compared the relative efficacy of the 5-hydroxytryptamine-3 (5-HT3) receptor antagonists.

Recommendations
Combined anthracycline and cyclophosphamide regimens were reclassified as highly emetic. Patients who receive this combination or any highly emetic agents should receive a 5-HT3 receptor antagonist, dexamethasone, and a neurokinin 1 (NK1) receptor antagonist. A large trial validated the equivalency of fosaprepitant, a single-day intravenous formulation, with aprepitant; either therapy is appropriate. Preferential use of palonosetron is recommended for moderate emetic risk regimens, combined with dexamethasone. For low-risk agents, patients can be offered dexamethasone before the first dose of chemotherapy. Patients undergoing high emetic risk radiation therapy should receive a 5-HT3 receptor antagonist before each fraction and for 24 hours after treatment. An update Committee noted the importance of continued symptom monitoring throughout therapy. Clinicians underestimate the incidence of nausea, which is not as well controlled as emesis.

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INTRODUCTION

The first American Society of Clinical Oncology (ASCO) guideline for the use of antiemetics was published in 1999 and updated once in 2006. This guideline provides clinicians with recommendations to prevent vomiting and nausea among patients undergoing antineoplastic therapy (chemotherapy-induced nausea and vomiting [CINV]) and/or radiation therapy (radiation-induced nausea and vomiting [RINV]) based on evidence from randomized clinical trials.

METHODS

An Update Committee (Appendix Table A1, online only) met twice to review data published since 2006 and update recommendations as warranted.

Literature Review

Literature search strategy. A systematic review on the effectiveness of newer antiemetics (aprepitant and the 5-hydroxytryptamine-3 [5-HT3] receptor antagonists), funded by the Agency for Healthcare Research and Quality, was initially reviewed for relevant publications. Two MEDLINE searches (search strategy available in the Data Supplement, http://www.asco.org/guidelines/antiemetics) were completed to identify additional randomized controlled trials; a search of the Cochrane Collaboration Library was also conducted. Meeting materials from the ASCO and Multinational Association of Supportive Care in Cancer annual meetings available since the 2006 update were additionally culled. Only full presentations or posters were eligible; material available only in abstract form was not considered.

Inclusion and exclusion criteria. Systematic reviews and reports from randomized controlled trials eligible for inclusion met the following criteria: the intervention was for the treatment of nausea or vomiting secondary to antineoplastic therapy (chemotherapy-induced nausea and vomiting [CINV]) and/or radiation therapy (radiation-induced nausea and vomiting [RINV]).
American Society of Clinical Oncology Clinical Practice Guideline Update on Antiemetics

**Intervention**

- Antiemetics for patients receiving cancer therapy.

**Target Audience**

- Medical Oncologists, Radiation Oncologists, Oncology Nurses.

**Key Recommendations**

- Patients who receive highly emetic chemotherapy regimens should receive the three-drug combination of a neurokinin 1 (NK₁) antagonist, 5-hydroxytryptamine-3 (5-HT₃) antagonist, and dexamethasone.
- The preferred 5-HT₃ antagonist for patients who receive moderate emetic chemotherapy regimens is palonosetron; antiemetic treatment includes that agent combined with a corticosteroid.
- Antiemetic treatment for patients who receive combination chemotherapy should be determined according to the agent with the greatest degree of emetic risk.
- Both dexamethasone and a 5-HT₃ antagonist are recommended for patients undergoing high-dose chemotherapy.
- Pediatric patients receiving either high or moderate emetic risk chemotherapy should be treated with a 5-HT₃ antagonist and corticosteroids; higher weight-based dosing may be required.
- For those treated with high emetic risk radiation therapy, a 5-HT₃ antagonist before each fraction and a 5-day course of dexamethasone are recommended.
- A 5-HT₃ antagonist before each fraction is also recommended before moderate-risk radiation; a 5-day course of dexamethasone is optional.
- For patients who receive combination chemoradiotherapy, antiemetic therapy is dictated by the emetogenicity of chemotherapy, unless the emetic risk of radiation therapy is higher.

**Methods**

- A systematic review of the literature published since the last update of the guideline.

The data supplement, including evidence tables and clinical tools and resources, can be found at www.asco.org/guidelines/antiemetics.
## Table 1. Summary of Recommendations

<table>
<thead>
<tr>
<th>Clinical Situation</th>
<th>2006 Recommendation</th>
<th>2011 Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemotherapy-induced nausea and vomiting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Highly emetogenic agents</strong></td>
<td>The three-drug combination of a 5-HT₃ receptor antagonist, dexamethasone, and aprepitant is recommended before chemotherapy. In all patients receiving cisplatin and all other agents of high emetic risk other than AC, we recommend the two-drug combination of a 5-HT₃ receptor antagonist and dexamethasone. In patients receiving AC, aprepitant as a single agent is recommended on days 2 and 3. For all other chemotherapies of moderate emetic risk, single-agent dexamethasone or a 5-HT₃ receptor antagonist is suggested for the prevention of emesis on days 2 and 3.</td>
<td>The three-drug combination of an NK₁ receptor antagonist (days 1-3 for aprepitant; days 1 only for fosaprepitant), a 5-HT₃ receptor antagonist (day 1 only), and dexamethasone (days 1-3) is recommended for patients receiving highly emetogenic chemotherapy. This recommendation is unchanged since the 2006 update, but reworded for clarification. The Update Committee also recommended reclassification of the combined AC regimen as highly emetogenic.</td>
</tr>
<tr>
<td><strong>Moderately emetogenic agents</strong></td>
<td>The three-drug combination of a 5-HT₃ receptor antagonist, dexamethasone, and aprepitant is recommended for patients receiving AC. For patients receiving chemotherapy of moderate emetic risk other than AC, we recommend the two-drug combination of a 5-HT₃ receptor antagonist and dexamethasone. In patients receiving AC, aprepitant as a single agent is recommended on days 2 and 3. For all other chemotherapies of moderate emetic risk, single-agent dexamethasone or a 5-HT₃ receptor antagonist is suggested for the prevention of emesis on days 2 and 3.</td>
<td>The two-drug combination of palonosetron (day 1 only) and dexamethasone (days 1-3) is recommended for patients receiving moderately emetogenic chemotherapy. If palonosetron is not available, clinicians may substitute a first-generation 5-HT₃ serotonin receptor antagonist, preferably granisetron or ondansetron. Limited evidence also supports adding aprepitant to the combination. Should clinicians opt to add aprepitant in patients receiving moderate-risk chemotherapy, any one of the 5-HT₃ antagonists is appropriate.</td>
</tr>
<tr>
<td><strong>Low emetogenic agents</strong></td>
<td>Dexamethasone 8 mg is suggested. No routine preventive use of antiemetics for delayed emesis is suggested.</td>
<td>A single 8-mg dose of dexamethasone before chemotherapy is suggested. No change since 2006.</td>
</tr>
<tr>
<td><strong>Minimally emetogenic agents</strong></td>
<td>No change from the original guideline. No antiemetic should be administered routinely before or after chemotherapy.</td>
<td>No antiemetic should be administered routinely before or after chemotherapy. No change from the original guideline.</td>
</tr>
<tr>
<td><strong>Combination chemotherapy</strong></td>
<td>No change from the original guideline. Patients should be administered antiemetics appropriate for the component chemotherapeutic (antineoplastic) agent of greatest emetic risk.</td>
<td>Patients should be administered antiemetics appropriate for the component chemotherapeutic (antineoplastic) agent of greatest emetic risk. No change from the original guideline.</td>
</tr>
<tr>
<td><strong>Adjunctive drugs</strong></td>
<td>Lorazepam and diphenhydramine are useful adjuncts to antiemetic drugs but are not recommended as single agents.</td>
<td>Lorazepam or diphenhydramine are useful adjuncts to antiemetic drugs but are not recommended as single-agent antiemetics. No change since 2006.</td>
</tr>
<tr>
<td><strong>Complementary therapy</strong></td>
<td>New question for 2011 update.</td>
<td>No published randomized controlled trial data that met inclusion criteria are currently available to support a recommendation about such therapies.</td>
</tr>
<tr>
<td><strong>Pediatric patients</strong></td>
<td>The combination of a 5-HT₃ antagonist plus a corticosteroid is suggested before chemotherapy in children receiving chemotherapy of high or moderate emetic risk. Because of variation of pharmacokinetic parameters in children, higher weight-based doses of 5-HT₃ antagonists than those used in adults may be required for antiemetic protection.</td>
<td>The combination of a 5-HT₃ antagonist plus a corticosteroïd is suggested before chemotherapy in children receiving chemotherapy of high or moderate emetic risk. Because of variation of pharmacokinetic parameters in children, higher weight-based doses of 5-HT₃ antagonists than those used in adults may be required for antiemetic protection. No change since 2006.</td>
</tr>
<tr>
<td><strong>High-dose chemotherapy with stem-cell or bone marrow transplantation</strong></td>
<td>No change from original guideline. A 5-HT₃ receptor antagonist antiemetic combined with dexamethasone is suggested. Aprepitant should be considered, although evidence to support its use specifically in these patients is lacking.</td>
<td>A 5-HT₃ receptor antagonist combined with dexamethasone is suggested. Aprepitant should be considered, although evidence to support its use is limited.</td>
</tr>
<tr>
<td><strong>Multiday chemotherapy</strong></td>
<td>No change from the original guideline. It is suggested that antiemetics appropriate for the risk class of the chemotherapy, as outlined earlier, be administered for each day of the chemotherapy and for 2 days after, if appropriate.</td>
<td>It is suggested that antiemetics appropriate for the emetogenic risk class of the chemotherapy be administered for each day of the chemotherapy and for 2 days after, if appropriate. No change from the original guideline. The Update Committee suggests, based on limited data, that patients receiving 5-day cisplatin regimens be treated with a 5-HT₃ antagonist in combination with dexamethasone and aprepitant.</td>
</tr>
<tr>
<td><strong>Emesis or nausea despite optimal prophylaxis</strong></td>
<td>No change from original guideline. The Update Committee suggests that clinicians conduct a careful re-evaluation of emetic risk, disease status, concurrent illnesses, and medications; ascertain that the best regimen is being administered for the emetic risk; consider adding lorazepam or alprazolam to the regimen; and consider substituting a high-dose intravenous metoclopramide for the 5-HT₃ antagonist or adding a dopamine antagonist to the regimen.</td>
<td>Clinicians should re-evaluate emetic risk, disease status, concurrent illnesses, and medications; ascertain that the best regimen is being administered for the emetic risk; consider adding lorazepam or alprazolam to the regimen; and consider adding olanzapine to the regimen or substituting high-dose intravenous metoclopramide for the 5-HT₃ antagonist or adding a dopamine antagonist to the regimen.</td>
</tr>
<tr>
<td><strong>Anticipatory nausea and vomiting</strong></td>
<td>No change since the original guideline. Use of the most active antiemetic regimens appropriate for the chemotherapy being administered to prevent acute or delayed emesis is suggested. Such regimens may be used with the initial chemotherapy, rather than assessing the patient’s emetic response with less effective treatment. If anticipatory emesis occurs, behavioral therapy with systematic desensitization is effective and suggested.</td>
<td>Use of the most active antiemetic regimens appropriate for the chemotherapy being administered to prevent acute or delayed emesis is suggested. Such regimens should be used with initial chemotherapy, rather than assessing the patient’s emetic response with less effective treatment. If anticipatory emesis occurs, behavioral therapy with systematic desensitization is effective and suggested. No change since the original guideline.</td>
</tr>
</tbody>
</table>

(continued on following page)
The pilot study by Herrington et al\textsuperscript{4} compared two dosing schedules of aprepitant (1 day vs 3 days). No differences in rates of complete response and emetic episodes for the overall study period were reported. Studies to validate the noninferiority of single-day oral aprepitant are necessary to establish equivalence.

A pilot study compared olanzapine with aprepitant.\textsuperscript{9} Patients randomly assigned to olanzapine experienced similar complete response rates as patients who received aprepitant. Olanzapine was superior for nausea control during the overall study period ($P < .01$). Additional trials are necessary to define the role of olanzapine in this setting.

The AC combination was reclassified based on the high emetic potential of the combined agents. Data from placebo-controlled studies indicate that this combination causes vomiting in 85% of patients not receiving antiemetic prophylaxis.\textsuperscript{9} This borders on the cutoff defined for highly emetogenic agents.\textsuperscript{9}

**Clinical Question 2**

What is the optimal treatment to prevent nausea and vomiting from moderately emetogenic antineoplastic agents?

**Recommendation 2.** The two-drug combination of palonosetron (day 1 only) and dexamethasone (days 1 through 3) is recommended for patients receiving moderately emetogenic chemotherapy. If palonosetron is not available, clinicians may substitute a first-generation 5-HT\textsubscript{3} receptor antagonist, preferably granisetron or ondansetron.

Limited evidence also supports adding aprepitant to the combination. Should clinicians opt to add aprepitant in patients receiving moderate-risk chemotherapy, any one of the 5-HT\textsubscript{3} antagonists is appropriate.

**Literature update and analysis 2a: 5-HT\textsubscript{3} receptor antagonist equivalency.** The Update Committee evaluated therapeutic equivalence of the 5-HT\textsubscript{3} receptor antagonists (ondansetron, granisetron, dolasetron, palonosetron, ramosetron, and tropisetron). A Cochrane Review of 5-HT\textsubscript{3} antagonists used to prevent CINV was identified.\textsuperscript{10} Most trials compared ondansetron and granisetron. Few trials including dolasetron and tropisetron were identified, and only one study with palonosetron was included,\textsuperscript{11} which is described in this section. No studies on ramosetron were included. Findings from the review suggest equivalency between ondansetron and granisetron, supported by a meta-analysis (Data Supplement). Another meta-analysis from Jordan et al\textsuperscript{12} assessed only first-generation 5-HT\textsubscript{3} receptor antagonists. This study also indicates equivalency of granisetron and ondansetron and superiority of granisetron compared with tropisetron.

A study comparing ramosetron and granisetron was identified.\textsuperscript{13} Findings indicate similar rates of complete response during the first 24 hours after chemotherapy. Research describing the efficacy of ramosetron during the 7-day period after chemotherapy is not available.

Three studies compared palonosetron with first-generation 5-HT\textsubscript{3} antagonists.\textsuperscript{11,14,15} Findings from two larger studies\textsuperscript{11,16} suggested that palonosetron provides superior protection against both nausea and vomiting, particularly during the period from 24 to 120 hours after chemotherapy. However, the third study yielded nonsignificant differences, which might be explained by the fact that it was designed as a noninferiority trial.\textsuperscript{15}

These studies were conducted in combined emetic risk populations, but not a non-AC moderately emetogenic population, and compared palonosetron with a first-generation 5-HT\textsubscript{3} receptor antagonist in which dexamethasone has also been included. The preference for palonosetron is an extrapolation from the Saito et al\textsuperscript{11} data; when ondansetron is superior to granisetron and dexamethasone. By inference, with non-AC moderately emetogenic chemotherapy, palonosetron
and dexamethasone are also likely to be superior to a first-generation 5-HT₃ receptor antagonist and dexamethasone.

**Literature update and analysis 2b: NK₁ receptor antagonist for moderately emetogenic chemotherapy.** One trial evaluated the utility of aprepitant in patients undergoing moderately emetogenic chemotherapy. Improved CINV protection with aprepitant was noted. An advantage of using aprepitant with moderate-risk agents is abbreviated dexamethasone dosing.

**Literature update and analysis 2c: Dexamethasone dosing.** Two trials evaluated dexamethasone dosing, comparing 1- and 3-day dexamethasone dosing combined with palonosetron. Findings from these trials suggest similar outcomes with the two regimens. Additional trials that validate these findings may warrant a change to the current recommendation.

**Clinical Question 3**

What is the optimal treatment to prevent nausea and vomiting from low emetogenic antineoplastic agents?

**Recommendation 3.** A single 8-mg dose of dexamethasone before chemotherapy is suggested.

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**Table 2. Emetic Risk of Intravenous Antineoplastic Agents**

<table>
<thead>
<tr>
<th>Emetic Risk</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Carmustine, Cisplatin, Cyclophosphamide ≥ 1,500 mg/m², Daclizumab, Dactinomycin, Mechlorethamine, Streptozocin</td>
</tr>
<tr>
<td>Moderate</td>
<td>Azactidine, Alemtuzumab, Bendamustine, Carboplatin, Clofarabine, Cyclophosphamide &lt; 1,500 mg/m², Cytarabine &gt; 1,000 mg/m², Daunorubicin*, Doxorubicin*, Etopubic*, Idarubicin*, Ifosfamide, Irinotecan, Oxaliplatin</td>
</tr>
<tr>
<td>Low</td>
<td>Fluorouracil, Bortezomib, Cabazitaxel, Catumaxomab, Cytarabine ≤ 1,000 mg/m², Docetaxel, Doxorubicin HCL liposome injection, Etoposide, Gemcitabine, Ifosfamide, Methotrexate, Mitomycin, Mitoxantrone, Paclitaxel, Panitumumab, Pemetrexed, Temsirolimus, Topotecan, Trastuzumab</td>
</tr>
<tr>
<td>Minimal</td>
<td>2-Chlorodeoxyadenosine, Bevacizumab, Bleomycin, Busulfan, Cetuximab, Fluorouracil, Fludarabine, Pralatrexate, Rituximab, Vinblastine, Vincristine, Vinorelbine</td>
</tr>
</tbody>
</table>

**Table 3. Antiemetic Dosing by Chemotherapy Risk Category**

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Dosing on Day of Chemotherapy</th>
<th>Dosing on Subsequent Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>High emetic risk*</td>
<td>Aprepitant 125 mg oral 80 mg oral; days 2 and 3</td>
<td>Fosaprepitant 150 mg IV</td>
</tr>
<tr>
<td>High emetic risk*</td>
<td>5-HT₃ antagonist Granisetron 2 mg oral; 1 mg or 0.01 mg/kg IV</td>
<td>Palonosetron 0.50 mg oral; 0.25 mg IV Dolasetron 100 mg oral ONLY</td>
</tr>
<tr>
<td>High emetic risk*</td>
<td>5-HT₃ antagonist Granisetron 2 mg oral; 1 mg or 0.01 mg/kg IV</td>
<td>Ondansetron 8 mg or 0.15 mg/kg IV</td>
</tr>
<tr>
<td>High emetic risk*</td>
<td>5-HT₃ antagonist Palonosetron 0.50 mg oral; 0.25 mg IV</td>
<td>Dolasetron 100 mg oral ONLY</td>
</tr>
<tr>
<td>High emetic risk*</td>
<td>5-HT₃ antagonist Palonosetron 0.50 mg oral; 0.25 mg IV</td>
<td>Ramosetron 0.3 mg IV</td>
</tr>
<tr>
<td>High emetic risk*</td>
<td>5-HT₃ antagonist Palonosetron 0.50 mg oral; 0.25 mg IV</td>
<td>Corticosteroid Dexamethasone 12 mg oral or IV 8 mg oral or IV; days 2-3 or days 2-4</td>
</tr>
<tr>
<td>Moderate emetic risk‡</td>
<td>5-HT₃ antagonist Palonosetron 0.50 mg oral; 0.25 mg IV</td>
<td>Corticosteroid Dexamethasone 8 mg oral or IV 8 mg; days 2 and 3</td>
</tr>
<tr>
<td>Low emetic risk</td>
<td>Corticosteroid Dexamethasone 8 mg oral or IV</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** For patients receiving multiday chemotherapy, clinicians must first determine the emetic risk of the agent(s) included in the regimen. Patients should receive the agent of the highest therapeutic index daily during chemotherapy and for 2 days thereafter. Patients can also be offered the granisetron transdermal patch that delivers therapy over multiple days rather than taking a serotonin antagonist daily. Abbreviations: 5-HT₃, 5-hydroxytryptamine-3; IV, intravenous; NK₁, neurokinin 1. *Includes combination of an anthracycline and cyclophosphamide. †The dexamethasone dose is for patients who are receiving the recommended three-drug regimen for highly emetogenic chemotherapy. If patients do not receive aprepitant, the dexamethasone dose should be adjusted to 20 mg on day 1 and 16 mg on days 2 to 4. ‡Clinicians who choose to use an NK₁ antagonist should follow high emetic risk chemotherapy dosing. Importantly, corticosteroid is only given on day 1; dexamethasone dose is 12 mg.

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Clinical Question 4
What is the optimal treatment to prevent nausea and vomiting from minimally emetogenic antineoplastic agents?

Recommendation 4. No antiemetic should be administered routinely before or after chemotherapy.

Literature update and analysis 4. No new evidence was identified.

Clinical Question 5
What is the optimal treatment to prevent nausea and vomiting from combination chemotherapy?

Recommendation 5. Patients should be administered antiemetics appropriate for the component chemotherapeutic (antineoplastic) agent of greatest emetic risk. AC combinations are now classified as highly emetogenic.

Literature update and analysis 5. No new evidence was identified.

Clinical Question 6
What is the role of adjunctive drugs for nausea and vomiting induced by cancer treatments?

Recommendation 6. Lorazepam and diphenhydramine are useful adjuncts to antiemetic drugs but are not recommended as single-agent antiemetics.

Literature update and analysis 6. One new trial evaluated the impact of including olanzapine in antiemetic regimens. Benefits of olanzapine were most evident during the days after chemotherapy.

Clinical Question 7
What is the role of complementary and alternative medicine therapies to prevent or control nausea and vomiting induced by chemotherapy?

Recommendation 7. No published randomized controlled trial data that met inclusion criteria are currently available to support a recommendation about such therapies.

Literature update and analysis 7. A phase III trial of ginger was presented at an ASCO meeting in 2009. No significant differences in the prevalence of vomiting and nausea between patients who received ginger and placebo were reported.

A Cochrane Systematic Review of acupuncture-point stimulation for CINV was published. However, this effort did not meet prespecified inclusion and exclusion criteria for this systematic review.

SPECIAL POPULATIONS
Clinical Question 8
What is the optimal treatment to prevent nausea and vomiting associated with cancer therapy for pediatric patients?

Recommendation 8. The combination of a 5-HT\textsubscript{3} antagonist plus a corticosteroid is suggested before chemotherapy in children receiving chemotherapy of high or moderate emetic risk. Because of the variation of pharmacokinetic parameters in children, higher weight-based doses of 5-HT\textsubscript{3} antagonists than those used in adults may be required for antiemetic protection. There is no change in this recommendation from 2006.

Literature update and analysis 8. A systematic review of available therapies for CINV in children was published by the Cochrane Collaboration. Few trials identified had similarities in intervention characteristics, so the review was primarily qualitative. A pooled analysis indicates that the addition of dexamethasone to the newer 5-HT\textsubscript{3} antagonists provides benefits in the high emetic risk setting.

Two trials were also identified. One assessed the use of aprepitant in this population. The second evaluated the efficacy and safety of palonosetron in pediatric patients.

Clinical Question 9
What is the optimal treatment to prevent nausea and vomiting in patients who are undergoing high-dose chemotherapy with stem-cell or bone marrow transplantation?

Recommendation 9. A 5-HT\textsubscript{3} receptor antagonist combined with dexamethasone is recommended. Aprepitant should be considered, although evidence to support its use is limited.

Literature update and analysis 9. Two new studies were identified. One report detailed superior emetic control with palonosetron. Data suggest that 2 days of palonosetron therapy will decrease the likelihood of CINV. The other trial evaluated use of aprepitant during chemotherapy conditioning. Patients who received aprepitant experienced markedly improved vomiting control.

Clinical Question 10
What is the optimal treatment to prevent nausea and vomiting for patients receiving multiday chemotherapy?

Recommendation 10. It is suggested that antiemetics appropriate for the emetogenic risk class of the chemotherapy be administered for each day of the chemotherapy and for 2 days after, if appropriate. There is no change from the original guideline.

Clinical Question 11
What is the optimal antiemetic regimen for patients who experience nausea and vomiting secondary to cancer therapy despite optimal prophylaxis?

Recommendation 11. Language from the 2006 guideline was reformatted for clarity. Clinicians should re-evaluate emetic risk, disease status, concurrent illnesses, and medications; ascertain that the best regimen is being administered for the emetic risk; consider adding lorazepam or alprazolam to the regimen; and consider adding olanzapine to the regimen or substituting high-dose intravenous metoclopramide for the 5-HT\textsubscript{3} antagonist or adding a dopamine antagonist to the regimen.

Literature update and analysis 11. No new evidence was identified.

Clinical Question 12
What treatment options are available for patients who experience anticipatory nausea and vomiting?

Recommendation 12. Use of the most active antiemetic regimens appropriate for the chemotherapy being administered to prevent acute or delayed emesis is suggested. Such regimens should be used with initial chemotherapy, rather than assessing the patient’s emetic response with less effective treatment. If anticipatory emesis
occurs, behavioral therapy with systematic desensitization is effective and suggested. No change since the original guideline.

Literature update and analysis 12. No new evidence was identified.

RADIATION-INDUCED NAUSEA AND VOMITING

An updated risk stratification table according to site of radiation treatment is provided in Table 4.29 Dosing schedules according to risk are listed in Table 5.

Clinical Question 13

What is the optimal prophylaxis for nausea and vomiting caused by high emetic risk radiation therapy?

Recommendation 13. On the basis of extrapolation from indirect evidence, the Update Committee recommends that all patients should receive a 5-HT₃ antagonist before each fraction and for at least 24 hours after completion of radiotherapy. Patients should also receive a 5-day course of dexamethasone during fractions 1 to 5.

Literature update and analysis 13. No new evidence was identified; the modification was based on evidence from the moderate-risk category.30

Clinical Question 14

What is the optimal prophylaxis for nausea and vomiting caused by moderate emetic risk radiation therapy?

Recommendation 14. The Update Committee recommends that patients receive a 5-HT₃ antagonist before each fraction for the entire course of radiotherapy. Patients may be offered a short course of dexamethasone during fractions 1 to 5.

Literature update and analysis 14. A new trial that evaluated the efficacy of adding 5 days of dexamethasone during radiation to the upper abdomen was identified.30 The addition of dexamethasone provided superior vomiting protection and lower average nausea, both secondary end points.

Clinical Question 15

What is the optimal treatment to manage nausea and vomiting associated with low emetic risk radiation therapy?

Recommendation 15. The Update Committee recommends a 5-HT₃ antagonist alone as either prophylaxis or rescue. For patients

### Table 4. Emetic Risk by Site of Radiation Therapy

<table>
<thead>
<tr>
<th>Emetic Risk</th>
<th>Site of Radiation Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Total-body irradiation</td>
</tr>
<tr>
<td></td>
<td>Total nodal irradiation</td>
</tr>
<tr>
<td>Moderate</td>
<td>Upper abdomen</td>
</tr>
<tr>
<td></td>
<td>Upper body irradiation</td>
</tr>
<tr>
<td></td>
<td>Half-body irradiation</td>
</tr>
<tr>
<td>Low</td>
<td>Cranium</td>
</tr>
<tr>
<td></td>
<td>Craniospinal</td>
</tr>
<tr>
<td></td>
<td>Head and neck</td>
</tr>
<tr>
<td></td>
<td>Lower thorax region</td>
</tr>
<tr>
<td></td>
<td>Pelvis</td>
</tr>
<tr>
<td>Minimal</td>
<td>Extremities</td>
</tr>
<tr>
<td></td>
<td>Breast</td>
</tr>
</tbody>
</table>

Data adapted.29

### Table 5. Antiemetic Dosing by Radiation Risk Category

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Dose</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>High emetic risk</td>
<td>5-HT₃ antagonist</td>
<td>5-HT₃ antagonist before each fraction throughout XRT; continue for at least 24 hours after completion of XRT</td>
</tr>
<tr>
<td>5-HT₃ antagonist</td>
<td>Granisetron†</td>
<td>2 mg oral; 1 mg or 0.01 mg/kg IV</td>
</tr>
<tr>
<td>5-HT₃ antagonist</td>
<td>Ondansetron†</td>
<td>8 mg oral twice daily; 8 mg or 0.15 mg/kg IV</td>
</tr>
<tr>
<td>5-HT₃ antagonist</td>
<td>Palonosetron†</td>
<td>0.50 mg oral; 0.25 mg IV</td>
</tr>
<tr>
<td>5-HT₃ antagonist</td>
<td>Dolasetron</td>
<td>100 mg oral only</td>
</tr>
<tr>
<td>5-HT₃ antagonist</td>
<td>Tropisetron</td>
<td>5 mg oral or IV</td>
</tr>
<tr>
<td>Corticosteroid</td>
<td>Dexamethasone</td>
<td>4 mg oral or IV</td>
</tr>
<tr>
<td>Moderate emetic risk</td>
<td>5-HT₃ antagonist</td>
<td>5-HT₃ antagonist before each fraction throughout XRT</td>
</tr>
<tr>
<td>5-HT₃ antagonist</td>
<td>Any of the above listed agents are acceptable; note preferred options†</td>
<td></td>
</tr>
<tr>
<td>Corticosteroid</td>
<td>Dexamethasone</td>
<td>4 mg IV or oral</td>
</tr>
<tr>
<td>Low emetic risk</td>
<td>5-HT₃ antagonist</td>
<td>5-HT₃ either as rescue or prophylaxis; if rescue is used, then prophylactic therapy should be given until the end of XRT</td>
</tr>
<tr>
<td>5-HT₃ antagonist</td>
<td>Any of the above listed agents are acceptable; note preferred options</td>
<td></td>
</tr>
<tr>
<td>Minimal emetic risk</td>
<td>5-HT₃ antagonist</td>
<td>Patients should be offered either class as rescue therapy; if rescue is used, then prophylactic therapy should be given until the end of XRT</td>
</tr>
<tr>
<td>5-HT₃ antagonist</td>
<td>Any of the above listed agents are acceptable; note preferred options</td>
<td></td>
</tr>
<tr>
<td>Dopamine receptor antagonist</td>
<td>Metoclopramide</td>
<td>20 mg oral</td>
</tr>
<tr>
<td>5-HT₃ antagonist</td>
<td>Prochlorperazine</td>
<td>10 oral or IV</td>
</tr>
</tbody>
</table>

Abbreviations: 5-HT₃, 5-hydroxytryptamine-3; IV, intravenous; XRT, radiation therapy.

†Preferred agents.

†No data are currently available on the appropriate dosing frequency with palonosetron in this setting. The Update Committee suggests that dosing every second or third day may be appropriate for this agent.
who experience RINV while receiving rescue therapy only, prophylactic treatment should continue until radiotherapy is complete.

**Clinical Question 16**

What is the optimal treatment to manage nausea and vomiting associated with minimal emetic risk radiation therapy?

**Recommendation 16.** Patients should receive rescue therapy with either a dopamine receptor antagonist or a 5-HT₃ antagonist. Prophylactic antiemetics should continue throughout radiation treatment if a patient experiences RINV while receiving rescue therapy.

**Literature update and analysis 16.** No new evidence was identified.

**Clinical Question 17**

What is the optimal treatment to manage nausea and vomiting during concurrent radiation and chemotherapy?

**Recommendation 17.** Patients should receive antiemetic prophylaxis according to the emetogenicity of chemotherapy, unless the emetic risk with the planned radiotherapy is higher. There is no change from the original guideline.

**Literature update and analysis 17.** No new evidence was identified.

**Drug Formulations and Agent Dosing**

Since the last update, an orally disintegrating ondansetron tablet became available.³¹ The orally disintegrating form is equivalent with respect to both emesis and nausea control. This is an acceptable alternative to the standard tablet.

Two other antiemetic agents received regulatory approval. As discussed, the granisetron transdermal patch is an option for patients who receive high-risk, multiday chemotherapy. The Update Committee suggests that this agent can also be considered for high- or moderate-risk radiation.

Palonosetron is now available orally.³² A noninferiority trial documented similarity between the oral and intravenous formulations and validated the dose for the agents when taken orally.³³

**PATIENT AND CLINICIAN COMMUNICATION**

The purpose of this section is to address aspects of patient-provider communication that are relevant to decision making regarding selection of antiemetic therapy. Clinicians are encouraged to provide patients with a prescription for a rescue antiemetic therapy before the patient leaves on the first day of treatment.

Data suggest that physicians frequently underestimate rates of nausea and vomiting secondary to radiation therapy and chemotherapy.³⁴ To ensure optimal symptom management, clinicians should assess symptoms throughout therapy. Patient response to antiemetic treatment may change over time, requiring ongoing assessments and modification to antiemetic strategies, as warranted.

Checklists can facilitate collection of direct patient reporting of symptom presence and severity. For example, the National Cancer Institute is developing a Patient-Reported Outcomes version of its Common Terminology Criteria for Adverse Events, which includes two items to assess nausea.³⁵ These items are as follows: “In the last 7 days, how OFTEN did you have NAUSEA?” (Never/Rarely/Occasionally/Frequently/Always most constantly) and “In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?” (None/Mild/Moderate/Severe/Very severe).

Clinicians and patients are also encouraged to discuss cost of treatment (Table 6) to assess whether cost is prohibitive, a hardship to patients, or may impact treatment compliance.

**HEALTH DISPARITIES**

ASCO clinical practice guidelines represent evidence-based expert recommendations on best practices to provide the highest level of cancer care. However, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Racial/ethnic minority patients with cancer suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured or underinsured, and are at greater risk of receiving care of poor quality compared with other Americans.³⁶–³⁹ Other patients lack access to care because of geography and, specifically, distance from appropriate treatment facilities. Other factors associated with disparities include advanced age, low educational attainment, and low socioeconomic status. Awareness of these disparities should be considered. Health care providers should strive to consider the factors faced by vulnerable populations to ensure that all patients receive the highest level of cancer care.

**FUTURE DIRECTIONS**

For most patients, antiemetic regimens prevent emesis and lessen nausea while patients are undergoing cancer therapy. However, some patients continue to report nausea.⁴⁰ Identification of new approaches to decrease nausea is required. Limited research on nausea and vomiting control in special populations is available, particularly pediatric patients. Similarly, few randomized controlled trials have investigated the role of antiemetics...
in patients undergoing radiation therapy. Research to improve symptom control in these patients is necessary.

The Update Committee recommends that studies that include nausea as an outcome include patient-reported measures of nausea, consistent with recommendations of the US Food and Drug Administration. Standardized approaches to assess nausea should be used across trials, which will allow for improved ability to compare regimens and trial data.

REFERENCES


AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a “U” are those for which no compensation was received; those relationships marked with a “C” were compensated. For a detailed description of the disclosure categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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AUTHOR CONTRIBUTIONS

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Antiemetics: ASCO Guideline Update

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controlled randomized trial of the National Cancer Institute of Canada Clinical Trials Group (SC19). J Clin Oncol 24:3458-3464, 2006


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Appendix

Table A1. Update Committee Members, 2011

<table>
<thead>
<tr>
<th>Member</th>
<th>Affiliation</th>
</tr>
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<tbody>
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<td>Paul J. Hesketh, MD, Steering Committee</td>
<td>Lahey Clinic Medical Center</td>
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<tr>
<td>Maurice Chesney</td>
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<td>Rowena N. Schwartz, PharmD, BCOP, CPP</td>
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