Guideline Summaries

Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update

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Journal of Clinical Oncology recently published ASCO's update to its antiemetics guideline.[1] ASCO first published an evidence-based clinical practice guideline on the use of antiemetics for patients with cancer in 1996. ASCO previously updated this guideline in 2006. For its current update, the scope remained largely unchanged and includes nausea and vomiting induced by chemotherapy, radiotherapy, and combination chemotherapy and radiation therapy. The scope now includes an evaluation of evidence on complementary antiemetic therapy.

The guideline is based on a systematic search and review of the literature. The Antiemetics Guideline Update Committee considered literature identified by a systematic review funded by the Agency for Healthcare Research and Quality. In addition to articles from the medical literature, both presentations and posters from the Multinational Association for Supportive Care in Cancer and ASCO Annual Meetings were eligible for inclusion. The primary efficacy outcomes of interest were complete response, emetic control, nausea control, and use of rescue antiemetics.

This most recent update reviews optimal therapy for patients receiving highly emetic chemotherapy, and 5-hydroxytryptamine 3 (5-HT_3) antagonist equivalency in the moderately emetogenic setting. Other key questions included the use of neurokinin 1 (NK_1) receptor antagonists in the moderately emetogenic and high-dose chemotherapy setting, treatment of radiation-induced nausea and vomiting, and antiemetic therapy for children. The update also reviews evidence regarding three new drug formulations approved by the US Food and Drug Administration since the 2006 update: fosaprepitant, an aprepitant prodrug (an NK_1 receptor antagonist); the granisetron transdermal system; and the ondansetron orally disintegrating tablet.

Other changes to recommendations for this update include those listed below. All of the 2006 and 2011 recommendations are listed in Table 1.

For chemotherapy-induced nausea and vomiting:

- Anthracyclines-cyclophosphamide combinations are reclassified as highly emetogenic.
- Palonosetron is preferred for use with patients receiving moderately emetogenic agents.
- Olanzapine may be added to the antiemetic regimen for patients who experience emesis or nausea despite optimal prophylaxis.
- In the evaluation of complementary therapy, the Update Committee found no published randomized trial data that met the inclusion and exclusion criteria.

For radiation-induced nausea and vomiting:

- A 5-day course of dexamethasone during fractions 1 to 5 is recommended for patients receiving high-risk radiotherapy.
- An optional 5-day course of dexamethasone during fractions 1 to 5 is recommended for patients receiving moderate-risk radiotherapy.
- For patients receiving low-risk radiotherapy, a 5-HT_3 receptor antagonist is recommended as either prophylaxis or rescue. In addition, patients requiring rescue should receive subsequent prophylactic antiemetic therapy.

Journal of Clinical Oncology published an Executive Summary of the Guideline Update[1]. The Executive Summary is brief overview of the complete ASCO Clinical Practice Guideline Update (available online only) and provides a brief discussion of the relevant literature for each recommendations. The complete Guideline Update—including expanded discussion of the literature, a description of methodology, and all cited references—and a Data Supplement with evidence tables and a patient guide are available at www.asco.org/guidelines/antiemetics. A slide set and a table with dosing information are provided in an online Data Supplement to this *JOP* article.

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Antiemetics: ASCO Clinical Practice Guideline Update was developed and written by Ethan Basch, Ann Alexis Prestrud, Paul J. Hesketh, Mark G. Kris, Petra C. Feyer, Mark R. Somerfield, Maurice Chesney, Rebecca Anne Clark-Snow, Anne Marie Flaherty, Barbara Freundlich, Gary Morrow, Kamakshi V. Rao, Rowena N. Schwartz, and Gary H. Lyman.

Accepted for publication on July 13, 2011.

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

Table 1. Summary of Recommendations

	2006	2011
Chemotherapy-induced nausea and vomiting		
Highly emetogenic agents	The three-drug combination of a 5-HT_3 receptor antagonist, dexamethasone, and aprepitant is recommended before chemotherapy. In all patients receiving cisplatin and all other agents of high emetic risk, the two-drug combination of dexamethasone and aprepitant is recommended. The Update Committee no longer recommends the combination of a 5-HT3 serotonin receptor antagonist and dexamethasone on days 2 and 3.	The three-drug combination of an NK_1 receptor antagonist (days 1-3 for aprepitant; day 1 only for fosaprepitant), a 5-HT_3 receptor antagonist (day 1 only), and dexamethasone (days 1-3 or 1-4) 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.
Moderately emetogenic agents	The three-drug combination of a 5-HT_3 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-HT_3 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-HT_3 receptor antagonist is suggested for the prevention of emesis on days 2 and 3.	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-HT_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_3 receptor antagonists is appropriate.
Low emetogenic agents	Dexamethasone 8 mg is suggested. No routine preventive use of antiemetics for delayed emesis is suggested.	A single 8-mg dose of dexamethasone before chemotherapy is suggested. No change since 2006.
Minimally emetogenic agents	No change from the original guideline. No antiemetic should be administered routinely before or after chemotherapy.	No antiemetic should be administered routinely before or after chemotherapy. No change from the original guideline.
Combination chemotherapy	No change from the original guideline. Patients should be administered antiemetics appropriate for the chemotherapeutic agent of greatest emetic risk.	Patients should be administered antiemetics appropriate for the component chemotherapeutic (antineoplastic) agent of greatest emetic risk. No change from the original guideline. AC combinations are now classified as highly emetogenic.
Adjunctive drugs	Lorazepam and diphenhydramine are useful adjuncts to antiemetic drugs, but are not recommended as single agents.	Lorazepam or diphenhydramine are useful adjuncts to antiemetic drugs but are not recommended as single-agent antiemetics. No change since 2006.
Complementary therapy	New question for 2011 update.	No published randomized controlled trial data that met inclusion criteria are currently available to support a recommendation about such therapies.
Pediatric patients	The combination of a 5-HT_3 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.	The combination of a 5-HT_3 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-HT_3 antagonists than those used in adults may be required for antiemetic protection. No change since 2006.
High-dose chemotherapy with stem cell or bone marrow transplant	No change from original guideline. A 5-HT_3 receptor antagonist antiemetic combined with dexamethasone is suggested. Aprepitant should be considered, although evidence to support its use specifically in these patients is lacking.	A 5-HT_3 receptor antagonist combined with dexamethasone is suggested. Aprepitant should be considered, although evidence to support its use is limited.
Multiday chemotherapy	No change from the original guideline. It is suggested that antiemetics appropriate for the risk class of the chemotherapy, as outlined above, be administered for each day of the chemotherapy and for 2 d after, if appropriate.	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-HT_3 receptor antagonist in combination with dexamethasone and aprepitant.
Emesis or nausea despite optimal prophylaxis	No change from original guideline. The Update Committee suggests that clinicians (1) conduct a careful re-evaluation of emetic risk, disease status, concurrent illnesses, and medications; (2) ascertain that the best regimen is being administered for the emetic risk; (3) consider adding lorazepam or alprazolam to the regimen; and (4) consider substituting a high-dose intravenous metoclopramide for the 5-HT_3 antagonist or adding a dopamine antagonist to the regimen.	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_3 antagonist or adding a dopamine antagonist to the regimen.

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Table 1. (Continued)

	2006	2011
Anticipatory nausea and vomiting	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.	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.
Radiation-induced nausea and vomiting		
High risk	No change from original guideline. The Update Committee suggests administration a 5-HT_3 antagonist with or without a corticosteroid before each fraction and for at least 24 h after. There is no change from the original guideline.	On the basis of extrapolation from indirect evidence, the Update Committee recommends that all patients should receive a 5-HT_3 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 1-5.
Moderate risk	The Update Committee recommends a 5-HT_3 antagonist before each fraction.	The Update Committee recommends that patients receive a 5-HT_3 antagonist before each fraction for the entire course of radiotherapy. Patients may be offered a short course of dexamethasone during fractions 1-5.
Low risk	No change from original guideline. The Update Committee recommends a 5-HT_3 antagonist before each fraction.	The Update Committee recommends a 5-HT_3 receptor antagonist alone as either prophylaxis or rescue. For patients who experience radiation-induced nausea and vomiting while receiving rescue therapy only, prophylactic treatment should continue until radiotherapy is complete.
Minimal risk	No change from original guideline. The Update Committee suggests that treatment be administered on an as-needed basis only. Dopamine or serotonin receptor antagonists are advised. Antiemetics should be continued prophylactically for each remaining radiation treatment day.	Patients should receive rescue therapy with either a dopamine receptor antagonist or a 5-HT_3 antagonist. Prophylactic antiemetics should continue throughout radiation treatment if a patient experiences radiation-induced nausea and vomiting while receiving rescue therapy.
Combined chemotherapy and radiation therapy	No change. Patients should receive rescue therapy with a dopamine-receptor antagonists or a 5-HT_3 receptor antagonist. Antiemetics should be continued prophylactically for each remaining radiation treatment day.	Patients should receive antiemetic prophylaxis according to the emetogenicity of chemotherapy, unless the emetic risk with the planned radiotherapy is higher. No change from the original guideline.

Abbreviations: AC, anthracycline and cyclophosphamide; 5-HT_3, 5-hydroxytryptamine-3; NK_1, neurokinin 1.

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.

Employment or Leadership Position: None **Consultant or Advisory Role:** Paul Joseph Hesketh, Merck (C), Eisai (C), GlaxoSmithKline (C), Helsinn (C); Mark G Kris, Sanofi-Aventis (C), GlaxoSmithKline (C) **Stock Ownership:** None **Honoraria:** None **Research Funding:** None **Expert Testimony:** None **Other Remuneration:** None

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DOI: 10.1200/JOP.2011.000397; posted online ahead of print at jop.ascopubs.org October 21, 2011.

Reference

1. Basch E, Prestrud AA, Hesketh P, et al: Antiemetics: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol [epub ahead of print on September 26, 2011]

THE BOTTOM LINE

ASCO *GUIDELINE UPDATE*

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 (NK_1) antagonist, 5-hydroxytryptamine-3 ($5\text{-}HT_3$) receptor antagonist, and dexamethasone.
- The preferred $5\text{-}HT_3$ receptor 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 $5\text{-}HT_3$ antagonist are recommended for patients undergoing high-dose chemotherapy.
- Pediatric patients receiving either high or moderate emetic risk chemotherapy should be treated with a $5\text{-}HT_3$ antagonist and corticosteroids; higher weight-based dosing may be required.
- For those treated with high emetic risk radiation therapy, a $5\text{-}HT_3$ antagonist before each fraction and a 5-day course of dexamethasone are recommended.
- A $5\text{-}HT_3$ 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.

Additional Information

- An Executive Summary of this guideline was published in *Journal of Clinical Oncology*

Data supplements, including evidence tables, and clinical tools and resources can be found at www.asco.org/guidelines/antiemetics.

Commentary: Should Cost and Comparative Value of Treatments Be Considered in Clinical Practice Guidelines?

By Ethan Basch, MD, MSc, Mark R. Somerfield, PhD, Ann Partridge, MD, MPH, Lowell Schnipper, MD, and Gary H. Lyman, MD, MPH

The cost of cancer treatment in the United States is increasing and has become a topic of national debate.[1] On average, US health care expenditures have grown more rapidly over the past three decades than in any other major industrialized nation. Cancer diagnostics and therapeutics constitute a substantial proportion of these costs. It is therefore critical to aggregate and evaluate evidence related to the effectiveness, safety, and relative value of treatments, toward informing clinical and policy decisions.

But it remains unclear which stakeholders in the continuum of oncology care— including policy makers, drug manufacturers, regulators, compendia developers, payers, specialty society–affiliated guideline developers, health care/hospital networks, clinicians, and/or patients—should participate in establishing whether a particular treatment or management approach offers better value for the money compared with other options (Table 1). Uneven attempts to define value, and lack of agreement on standards to do so, have led to inconsistent pricing and coverage policies.

For example, the Centers for Medicare & Medicaid Services (CMS) recently opted to continue coverage for bevacizumab (Avastin) in metastatic breast cancer despite results from randomized controlled trials that failed to demonstrate any survival advantage, and a unanimous vote by a US Food and Drug Administration (FDA) Advisory Committee not to sustain approval for this indication. CMS also recently conducted a review of coverage for Sipuleucel-T (Provenge) in metastatic