Fourth Consensus Guidelines for the Management of Postoperative Nausea and Vomiting

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This consensus statement presents a comprehensive and evidence-based set of guidelines for the care of postoperative nausea and vomiting (PONV) in both adult and pediatric populations. The guidelines are established by an international panel of experts under the auspices of the American Society of Enhanced Recovery and Society for Ambulatory Anesthesia based on a comprehensive search and review of literature up to September 2019. The guidelines provide recommendation on identifying high-risk patients, managing baseline PONV risks, choices for prophylaxis, and rescue treatment of PONV as well as recommendations for the institutional implementation of a PONV protocol. In addition, the current guidelines focus on the evidence for newer drugs (eg, second-generation 5-hydroxytryptamine 3 [5-HT_3] receptor antagonists, neurokinin 1 (NK1) receptor antagonists, and dopamine antagonists), discussion regarding the use of general multimodal PONV prophylaxis, and PONV management as part of enhanced recovery pathways. This set of guidelines have been endorsed by 23 professional societies and organizations from different disciplines (Appendix 1).

What Other Guidelines Are Available on This Topic?

Guidelines currently available include the 3 iterations of the consensus guideline we previously published, which was last updated 6 years ago[1–3]; a guideline published by American Society of Health System Pharmacists in 1999[4]; a brief discussion on PONV management as part of a comprehensive postoperative care guidelines[5]; focused guidelines published by the Society of Obstetricians and Gynecologists of Canada,[6] the Association of Paediatric Anaesthetists of Great Britain & Ireland[7] and the Association of Perianesthesia Nursing[8]; and several guidelines published in other languages.[9–12]

Why Was This Guideline Developed?

The current guideline was developed to provide perioperative practitioners with a comprehensive and up-to-date, evidence-based guidance on the risk stratification, prevention, and treatment of PONV in both adults and children. The guideline also provides guidance on the management of PONV within enhanced recovery pathways.

How Does This Guideline Differ From Existing Guidelines?

The previous consensus guideline was published 6 years ago with a literature search updated to October 2011. Several guidelines, which have been published since, are either limited to a specific populations[7] or do not address all aspects of PONV management.[13] The current guideline was developed based on a systematic review of the literature published up through September 2019. This includes recent studies of newer pharmacological agents such as the second-generation 5-hydroxytryptamine 3 (5-HT_3) receptor antagonists, a dopamine antagonist, neurokinin 1 (NK1) receptor antagonists as well as several novel combination therapies. In addition, it also contains an evidence-based discussion on the management of PONV in enhanced recovery pathways. We have also discussed the implementation of a general multimodal PONV prophylaxis in all at-risk surgical patients based on the consensus of the expert panel. (Anesth Analg 2020;131:411–48)

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GLOSSARY

5-HT$_3$ = 5-hydroxytryptamine 3; **AQI** = Anesthesiology Quality Institute; **ARR** = absolute risk reduction; **ASA** = American Society of Anesthesiologists; **ASER** = American Society for Enhanced Recovery; **BMI** = body mass index; **BP** = blood pressure; **CD** = cesarean delivery; **CER** = control event rate; **CI** = confidence interval; **CINV** = chemotherapy-induced nausea and vomiting; **CMS** = Centers for Medicare & Medicaid Services; **CNS** = central nervous system; **ERPs** = enhanced recovery pathways; **FDA** = Food and Drug Administration; **GA** = general anesthesia; **GABA** = γ-aminobutyric acid; **GI** = gastrointestinal; **HR** = heart rate; **IM** = intramuscular; **ISMP** = Institute of Safe Medication Practices; **IV** = intravenous(ly); **LOS** = length of stay; **MECIR** = Methodological Expectations of Cochrane Intervention Review; **MIPS** = merit-based incentive payment system; **NACOR** = National Anesthesia Clinical Outcomes Registry; **NK1** = neurokinin 1; **NNH** = number needed to harm; **NNT** = number needed to treat; **NPO** = nil per os; **NSAIDs** = nonsteroidal anti-inflammatory drugs; **ODT** = orally disintegrated tablet; **PACU** = postanesthesia care unit; **PC6** = pericardium 6 acupuncture point; **PCA** = patient-controlled analgesia; **PDNV** = postdischarge nausea and vomiting; **PECs** = pectoral nerves block; **PO** = per os; **POD** = postoperative day; **PONV** = postoperative nausea and vomiting; **POV** = postoperative vomiting; **POVOC** = Postoperative Vomiting in Children score; **PRESS** = Peer Review of Electronic Search Strategies; **PRISMA** = Preferred Reporting Items for Systematic Reviews and Meta-analyses; **PVB** = paravertebral block; **RA** = regional anesthesia; **RCT** = randomized controlled trials; **RRR** = relative risk reduction; **SRMA** = systematic review and meta-analysis; **TAP** = transversus abdominis plane block; **TIVA** = total intravenous anesthesia

Nausea and vomiting are two of the most common adverse events in the postoperative period with an estimated incidence of 30% in the general surgical population and as high as 80% in high risk cohorts.[14] This can be a highly distressing experience and is associated with significant patient dissatisfaction.[15,16] In addition, the occurrence of postoperative nausea and vomiting (PONV) is also associated with a significantly longer stay in the postanesthesia care unit (PACU),[17] unanticipated hospital admission,[18] and increased health care costs.[19]

Optimal management of PONV is a complex process. There are numerous antiemetics with varying pharmacokinetics, efficacy, and side-effect profiles, thus the choice of an antiemetic will depend on the clinical context. The benefit of PONV prophylaxis also needs to be balanced with the risk of adverse effects. At an institutional level, the management of PONV is also influenced by factors such as cost-effectiveness, drug availability, and drug formulary decisions. While there are several published guidelines on the management of PONV, they are limited to specific patient populations,[6,7] do not address all aspects of PONV management in sufficient detail,[5,13] or are not up to date with current literature.

Our group has previously published 3 iterations of the PONV consensus guideline in 2003, 2009, and 2014,[1–3] with the aim of providing comprehensive, evidence-based clinical recommendations on the management of a PONV in adults and children. A systematic literature search identified over 9000 published studies since the last consensus guideline (literature search up to October 2011). In addition, the establishment of enhanced recovery pathways (ERPs) has led to a significant paradigm shift in the approaches to perioperative care. We therefore present this update to incorporate the findings of the most recent studies into our recommendations.

METHODS

Goals of the Guidelines

The goals of the current guidelines were established by the panels as follows: (1) identify reliable predictors of PONV risks in adults and postoperative vomiting (POV) risk in children; (2) establish interventions which reduce the baseline risk for PONV; (3) assess the efficacy of individual antiemetic and combination therapies for PONV prophylaxis including nonpharmacological interventions; (4) ascertain the efficacy

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of PONV and postdischarge nausea and vomiting (PDNV) treatment with or without prior PONV prophylaxis; (5) determine the optimal dosing and timing of antiemetic prophylaxis; (6) appraise the cost-effectiveness of PONV management strategies; (7) create an algorithm to summarize the risk stratification, risk reduction, prophylaxis, and treatment of PONV; (8) evaluate the management of PONV within ERPs; and (9) propose a research agenda for future studies.

Establishment of the Expert Panel

The consensus guideline was established based on available published clinical evidence, which was reviewed by an international multidisciplinary expert panel. Panel members were invited on a basis of significant contributions in the field of PONV research or representation in professional societies with interest in PONV management, many of whom were also involved in the previous iterations of the guidelines. Panel members were asked to work in groups—each focusing on a given topic—and review the literature identified from the literature search. The first group assessed the risk factors for PONV. Two groups investigated the efficacy of pharmacological and nonpharmacological interventions for prophylaxis and treatment in adults. The fourth group reviewed the different combination therapies. The fifth group appraised the literature on antiemetic therapy within ERPs. The sixth group evaluated the literature on economics and designed the treatment algorithms. The seventh group analyzed pediatric antiemetic prophylaxis and treatment. The findings were then summarized and presented at the consensus meeting. After reviewing the evidence presented, the panel was then asked to reach a consensus on the interpretation and grading of the evidence as well as its clinical relevance. When a consensus was not reached, the majority view was presented, and the lack of full agreement was acknowledged in the guideline.

Literature Search and Review

With the help of a research librarian experienced in search strategy development (Marina Englesakis, University Health Network, Toronto, ON, Canada), who was working with a coauthor (F.C.) with input from the members of the consensus panel, a standardized literature search was performed to include publications from January 2011 to February 2019. Continued literature surveillance was done through September 2019. The searching process followed the Cochrane Handbook[20] and the Cochrane Methodological Expectations of Cochrane Intervention Reviews (MECIR)[21] for conducting the search, the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline[22,23] for reporting the search, and the Peer Review of Electronic Search Strategies (PRESS) guideline for peer-reviewing the search strategies.[24]

All of the following databases used were searched from the inception of the review over the Ovid platform for all topics: Ovid MEDLINE(R); Ovid MEDLINE(R) Epub Ahead of Print and In-Process & Other Non-Indexed Citations; Embase Classic+Embase; Cochrane Central Register of Controlled Trials; Cochrane Database of Systematic Reviews.

Preliminary searches were conducted, and full-text literature was mined for potential keywords and appropriate controlled vocabulary terms (Medical Subject Headings for Medline and EMTREE descriptors for Embase).

Our search was restricted to studies in adults ≥18 years of age and published in the English language with the exception of the search on pediatric antiemetic prophylaxis and treatment. All duplicate records were removed. Members of the team also manually searched the reference lists of included studies for other relevant studies. The relevant findings of the included studies were noted and aggregated according to the topic. The full search strategies used in Medline for the different questions are shown in Supplemental Digital Content, Appendix 2, http://links.lww.com/AA/D80.

Grading of Evidence

For the purposes of characterizing the quality of evidence for each intervention, we used a grading system similar to that in the previous guidelines (Table 1),[3] which was previously reported by the American Society of Anesthesiologists (ASA) in their acute pain management practice guideline.[3,25] This provides an objective standard against which clinical evidence could be compared.

RESULTS

Guideline 1. Identify Patients' Risk for PONV

Risk Factors. The previous guidelines identified independent risk factors that were significant in multivariable analyses of large cohort studies. Patient-specific risk factors for PONV in adults include female sex, a history of PONV and/or motion sickness, nonsmoking status, and young age (evidence B1).[14,26–31] Certain types of surgery may be associated with an increased risk of PONV including laparoscopic, bariatric, gynecological surgery, and cholecystectomy (evidence B1).[26,28,31–34] The main risk factors and their relative contribution are summarized in Figure 1.[35] As discussed in the previous versions of the guidelines, studies regarding other commonly discussed factors reported limited clinical value (eg, anxiety[36]), uncertain significance (eg, menstrual cycle,[37] neostigmine,[38,39] and perioperative fasting[40]), or demonstrated no association with PONV

Table 1. Quality of Clinical Evidence[3,25]

Category A: Supportive literature.
Randomized controlled trials report statistically significant differences between clinical interventions for a specified clinical outcome.[a]
- Level 1: The literature contains multiple randomized controlled trials, and aggregated findings are supported by meta-analysis.
- Level 2: The literature contains multiple randomized controlled trials, but the number of studies is insufficient to conduct a viable meta-analysis for the purpose of these guidelines.
- Level 3: The literature contains a single randomized controlled trial.

Category B: Suggestive literature.
Information from observational studies permits inference of beneficial or harmful relationships among clinical interventions and clinical outcomes.
- Level 1: The literature contains observational comparisons (eg, cohort, case-control research designs) of clinical interventions or conditions and indicates statistically significant differences between clinical interventions for a specified clinical outcome.
- Level 2: The literature contains noncomparative observational studies with associative (eg, relative risk, correlation) or descriptive statistics.
- Level 3: The literature contains case reports.

Category C: Equivocal literature.
The literature cannot determine whether there are beneficial or harmful relationships among clinical interventions and clinical outcomes.
- Level 1: Meta-analysis did not find significant differences ($P > .01$) among groups or conditions.
- Level 2: The number of studies is insufficient to conduct meta-analysis, and (1) randomized controlled trials have not found significant differences among groups or conditions or (2) randomized controlled trials report inconsistent findings.
- Level 3: Observational studies report inconsistent findings or do not permit inference of beneficial or harmful relationships.

Category D: Insufficient evidence from literature.
The lack of scientific evidence in the literature is described by the following terms.
- Inadequate: The available literature cannot be used to assess relationships among clinical interventions and clinical outcomes. The literature either does not meet the criteria for content as defined in the "Focus" of the Guidelines or does not permit a clear interpretation of findings due to methodological concerns (eg, confounding in study design or implementation).
- Silent: No identified studies address the specified relationships among interventions and outcomes.

Adapted with permission from the American Society of Anesthesiologists Task Force on Acute Pain Management, "Practice Guidelines for Acute Pain Management in the Perioperative Setting: An Updated Report by the American Society of Anesthesiologists Task Force on Acute Pain Management," *Anesthesiology*, 2012;116:248–273.[25]
[a]Statistical significance level was set at $P < .05$.

(eg, nasogastric tube, obesity, and supplemental oxygen[41–43]; Table 2).

Anesthetic risk factors of PONV include volatile anesthetics, nitrous oxide, and postoperative opioids (evidence A1).[26,44] The effect of volatile anesthetics on PONV was shown to be dose-dependent and particularly prominent in the first 2–6 hours following surgery.[26]

Irrespective of the specific opioid administered,[45,46] this drug class increases the risk for PONV in a dose-dependent manner,[47] and the effect appears to last for as long as opioids are used in the postoperative period.[27] The incidence of PONV is lower with opioid-free total intravenous anesthesia (TIVA),[48] multimodal pain management, opioid-free regional anesthesia (RA),[49] reduced opioid consumption,[50] perioperative administration of α_2 agonists,[51] and beta-blockers.[52]

The previous guidelines cited the use of nitrous oxide as a likely cause of PONV. A recent study found that the risk of PONV due to nitrous oxide appears to be duration dependent. In anesthesia lasting less than an hour, the number needed to treat (NNT) to prevent

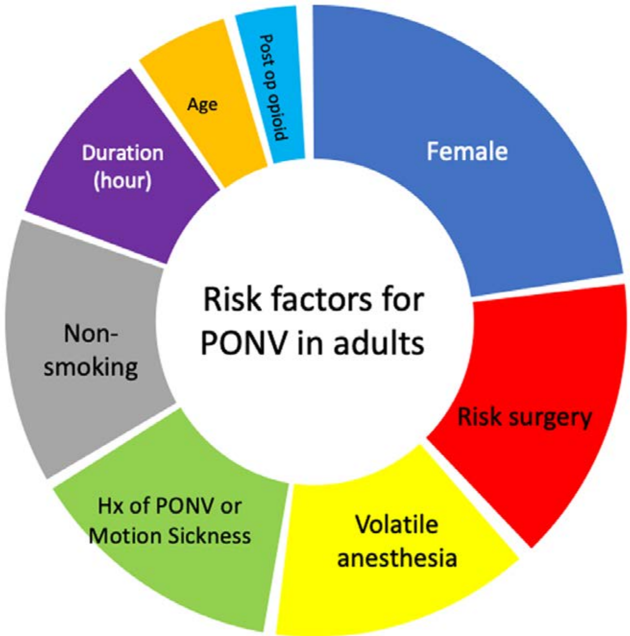

Figure 1. PONV risk factor summary. Intraoperative and postoperative risk factors of PONV in adults; the size of each segment is proportional to the odds ratios of PONV associated with each risk factors.[35] PONV indicates postoperative nausea and vomiting. The Figure reused with permission from the American Society for Enhanced Recovery. For permission requests, contact info@aserhq.org.

Table 2. Risk Factors for PONV in Adults

Evidence	Risk Factors
Positive overall	Female sex (B1)
	History of PONV or motion sickness (B1)
	Nonsmoking (B1)
	Younger age (B1)
	General versus regional anesthesia (A1)
	Use of volatile anesthetics and nitrous oxide[a] (A1)
	Postoperative opioids (A1)
	Duration of anesthesia (B1)
	Type of surgery (cholecystectomy, laparoscopic, gynecological) (B1)
Conflicting	ASA physical status (B1)
	Menstrual cycle (B1)
	Level of anesthesiologist's experience (B1)
	Perioperative fasting (A2)
Disproven or of limited clinical relevance	BMI (B1)
	Anxiety (B1)
	Nasogastric tube (A1)
	Migraine (B1)
	Supplemental oxygen (A1)

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; PONV, postoperative nausea and vomiting.
[a]Use of nitrous oxide over 1 h duration.

PONV from nitrous oxide avoidance is 128; the NNT decreases to 23 in anesthesia lasting over an hour, and to 9 in anesthesia lasting over 2 hours.[53] In addition, nitrous oxide is commonly used for labor analgesia and is associated with the risk of nausea and vomiting.[54] In patients who subsequently require emergency cesarean delivery (CD), the use of nitrous oxide may interact with the other perioperative PONV risk factors; however, this is not well studied.[55]

Enhanced recovery protocols have relaxed nil per os (NPO) status and fasting guidelines in regard to the impact on PONV. One study reported that NPO after midnight may increase the risk of PONV.[56]

Understanding of the PONV risk factors will allow for better risk assessment as well as better perioperative risk reduction.

Patient Risk Assessment for PONV. PONV risk factors should be used for risk assessment and to guide PONV management.[3] Several recent publications have challenged the utilization of risk factors to guide management and propose a more liberal administration of PONV prophylaxis in patients with lower risk of PONV.[3,57] The utility of this approach requires further validation with particular focus on the incidence of antiemetic side effects. The National Anesthesia Clinical Outcomes Registry (NACOR) and the Anesthesiology Quality Institute (AQI) created customized data on antiemetic prophylaxis, which has been evaluated and utilized as a marker of anesthesia quality and a measure of disparity in treatment.[58] The study found that 53% of the patients received ondansetron and/or dexamethasone prophylaxis, and only 17% received both ondansetron and dexamethasone. An objective assessment of risk factors should be taken into consideration to inform and adjust treatment.

Risk Scores. PONV risk scores have been shown to reduce the rate of PONV at an institutional level and can be used to inform and guide therapy.[59–61] Commonly used risk scores for inpatients undergoing anesthesia are the Koivuranta score and the Apfel score.[14,30] The Apfel simplified risk score is based on 4 predictors: female sex, history of PONV and/or motion sickness, nonsmoking status, and use of postoperative opioids (Figure 2).[14] The incidence of PONV with the presence of 0, 1, 2, 3, and 4 risk factors is approximately 10%, 20%, 40%, 60%, and 80%, respectively.[14] The panel classifies patients with 0–1, 2, or 3-plus risk factor into “low,” “medium,” and “high” risk categories, respectively. Koivuranta score includes the 4 Apfel risk predictors as well as length of surgery >60 minutes.[30] Some experts and limited publications have suggested 1 or 2 antiemetics should be administered to all patients since risk scores are not completely predictive.[3,57] Risk scores represent an objective approach to predict the incidence of PONV or PDNV, with sensitivity and specificity of between 65% and 70%, and should be utilized as a modifier for prophylaxis. If vomiting poses a significant medical

Risk Factors	Points
Female Gender	1
Non-Smoker	1
History of PONV and/or Motion Sickness	1
Postoperative Opioids	1
Sum of points	0-4

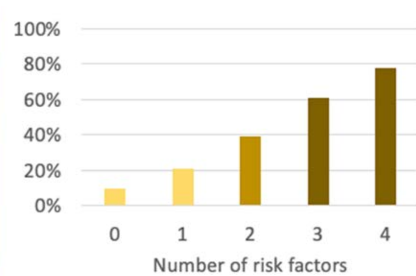

Figure 2. Risk score for PONV in adults. Simplified risk score from Apfel et al[14] to predict the patient’s risk for PONV. 0, 1, 2, 3, and 4 risk factors correspond to PONV risks of approximately 10%, 20%, 40%, 60%, and 80%, respectively. PONV indicates postoperative nausea and vomiting. The Figure reused with permission from the American Society for Enhanced Recovery. For permission requests, contact info@aserhq.org.

Risk Factors	Points
Female Gender	1
History of PONV	1
Age <50	1
Use of opioids in PACU	1
Nausea in PACU	1
Sum of points	0-5

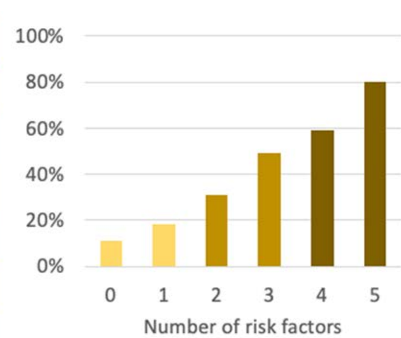

Figure 3. Risk score for PDNV in adults. Simplified risk score for PDNV in adults from Apfel et al[27] to predict the risk for PDNV in adults. 0, 1, 2, 3, 4, and 5 risk factors correspond to PDNV risks of approximately 10%, 20%, 30%, 50%, 60%, and 80%, respectively. PACU indicates postanesthesia care unit; PDNV, postdischarge nausea and vomiting; PONV, postoperative nausea and vomiting. The Figure reused with permission from the American Society for Enhanced Recovery. For permission requests, contact info@aserhq.org.

risk, such as an increased intracranial pressure, this should be further taken into consideration.

PDNV presents a significant risk to discharged patients who no longer have access to fast-onset intravenous (IV) antiemetics or direct care. A study of 2170 US outpatients reported the incidence of PDNV to be 37% in the first 48 hours after discharge and identified 5 independent predictors of PDNV, including female sex, age <50 years, history of PONV, opioid use in the PACU, and nausea in the PACU.[27] Validation of a simplified PDNV risk score based on these risk factors found that the incidence of PDNV with 0, 1, 2, 3, 4, or 5 of these risk factors to be about 10%, 20%, 30%, 50%, 60%, and 80%, respectively (Figure 3).[27]

Assessment for PONV/POV Risk in Children. A systematic review of the recent literature provided 53 relevant articles for pediatric patients since the publication of the 2014 PONV guidelines.[3] The 2019 review and analysis reemphasize the guideline recommendations from the 2014 consensus panel with stronger levels of evidence for each recommendation published since the previous update.

The risk factors for POV/PONV in children are different from those in adults[62–65] and are summarized in Figure 4. Children are more at risk for PONV/POV when they are older than 3 years, subjected to certain surgeries—namely tonsillectomy and eye surgeries, or are postpubertal females (evidence B1). The other risk factors are summarized in the aforementioned figure and have been validated by Kranke et al[66] by using the Postoperative Vomiting in Children (POVOC) score.[67–69]

Since the 2014 guidelines, there has been a paucity of new research investigating additional risk factors for

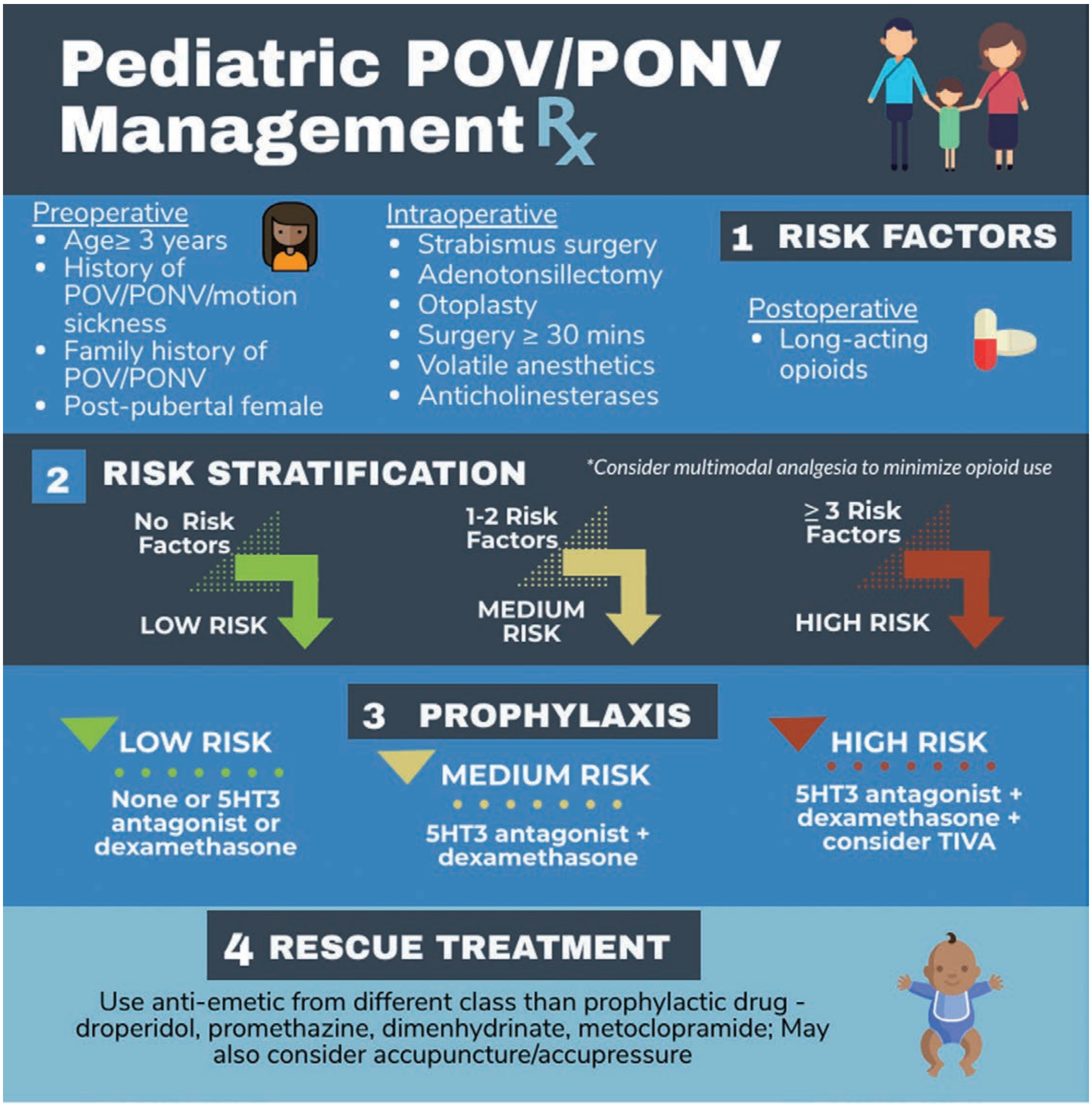

Figure 4. Algorithm for POV/PONV management in children. Summary of recommendations for POV/PONV management in children, including risk identification, risk-stratified prophylaxis, and treatment of established postoperative vomiting. 5-HT_3 indicates 5-hydroxytryptamine 3; PONV, postoperative nausea and vomiting; POV, postoperative vomiting; TIVA, total intravenous anesthesia. The Figure reused with permission from the American Society for Enhanced Recovery. For permission requests, contact info@aserhq.org.

Risk Factors	Points
Surgery ≥ 30 minutes	1
Age ≥ 3 years	1
Strabismus surgery	1
History of POV or family history of PONV	1
Sum of points	0-4

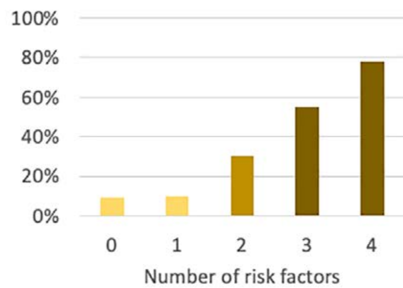

Figure 5. Risk score for POV in children. Simplified risk score from Eberhart et al[62] to predict the risk for POV in children. 0, 1, 2, 3, or 4 risk factors correspond to POV risks of approximately 10%, 10%, 30%, 50%, or 70%, respectively. PONV indicates postoperative nausea and vomiting; POV, postoperative vomiting. The Figure reused with permission from the American Society for Enhanced Recovery. For permission requests, contact info@aserhq.org.

Table 3. Strategies to Reduce Baseline Risk

Avoidance of GA by the use of regional anesthesia[31,65] (A1)
Use of propofol for induction and maintenance of anesthesia[70] (A1)
Avoidance of nitrous oxide in surgeries lasting over 1 h (A1)
Avoidance of volatile anesthetics[26,61] (A2)
Minimization of intraoperative (A2) and postoperative opioids[26,47,49,72] (A1)
Adequate hydration[73,74] (A1)
Using sugammadex instead of neostigmine for the reversal of neuromuscular blockade[75] (A1)

Abbreviation: GA, general anesthesia.

POV/PONV in children. As previously proposed by Eberhart et al,[62] POV risk in children can be predicted based on 4 criteria: duration of surgery >30 minutes; age >3 years; personal or first-degree relative history of POV/PONV; and strabismus surgery. Based on the presence of 0, 1, 2, 3, and 4 factors, the risk of POV was 9%, 10%, 30%, 55%, and 70%, respectively (Figure 5). This was subsequently verified by Kranke et al.[66]

Guideline 2. Reduce Baseline Risk for PONV

Discussion. Approaches for decreasing baseline risk are presented in Table 3. Strategies recommended to reduce baseline risk for PONV include (1) minimization of perioperative opioids with the use of multimodal analgesic regimens; (2) preferential use of RA; (3) preferential use of propofol infusions as the primary anesthetic[70,71]; (4) avoidance of volatile anesthetics; and (5) adequate hydration in patients undergoing same-day surgery (Table 3).

Multimodal Systemic Analgesia. Prophylactic IV acetaminophen as part of a multimodal analgesic regimen reduces nausea, only if given before the onset of pain (evidence A1).[76] After a gastrectomy, IV acetaminophen, in addition to continuous epidural analgesia, showed decreased opioid use and a significantly reduced incidence of PONV.[77] While oral acetaminophen has also been shown to reduce opioid requirement[78] and is considerably less costly, its effect on PONV is not well-studied.

Randomized controlled trials (RCTs) and meta-analyses show that perioperative nonsteroidal anti-inflammatory drugs, (NSAIDs) and cyclooxygenase-2 inhibitors[50,79,80] and less so intraoperative ketamine[81] may have a morphine-sparing effect in the postoperative period (evidence A1). An SRMA reported that, in patients with postoperative patient-controlled analgesia (PCA), IV or intramuscular (IM) NSAIDs significantly reduced the risk of PONV, and appears to be more effective than IV acetaminophen (evidence A1).[82] However, there are data to suggest that nonselective NSAIDs are associated with anastomotic leak in gastrointestinal (GI) surgery and should be used with caution.[83–85]

Perioperative Dexmedetomidine. Systemic α_2 agonists (clonidine or dexmedetomidine) administration decrease postoperative opioid consumption and PONV (evidence A1).[86] After laparoscopic cholecystectomy, dexmedetomidine 1 µg/kg before skin incision reduced the incidence of PONV similar to dexamethasone 8 mg and proved superior in lowering postoperative pain during the first 24 hours.[87] The same pain and PONV benefits were confirmed when dexmedetomidine was added to an IV sufentanil-ondansetron PCA after thoracotomy.[88] Prophylactic dexmedetomidine 0.5 µg/kg reduced postoperative pain at 1 hour and, on postoperative days (POD) 1–3, resulted in a faster return to daily activities in ambulatory urologic surgery under inhalation general anesthesia (GA). However, there was no difference versus the placebo in the incidence of PONV or use of antiemetics.[89] Similarly, intraoperative infusion of esmolol, a short-acting β-antagonist have been shown to reduce PACU opioid requirement as well as PONV risk (evidence A3).[52]

Neuraxial Anesthesia. A meta-analysis showed that epidural anesthesia significantly decreases the risk of PONV, whereas intrathecal opioids may promote PONV.[90] To be effective after gynecological surgery, epidural anesthesia administration may need to be continued after surgery and at a sufficient concentration (eg, lidocaine 10 mg/mL or equivalent).[91] After open colorectal cancer surgery, thoracic epidural anesthesia demonstrated significantly better pain control than IV morphine and with less PONV.[92] Bilateral transversus abdominis plane block (TAP) decreases postoperative opioid use and PONV after abdominal surgery. In colorectal surgery, compared to thoracic epidural anesthesia, the TAP blocks allowed for a shorter length of stay (LOS) without a difference in PONV.[93]

Regional Anesthesia. In colorectal surgery, continuous subfascial plane infusion of ropivacaine and fentanyl IV PCA demonstrated comparable risk of PONV (evidence A3).[94] Conversely, continuous local anesthetic wound infiltration or epidural anesthesia for 48 hours after open gastrectomy was associated with lower morphine consumption, less PONV, and a shorter LOS than morphine PCA (evidence A3).[95] In a review of 18 studies that compared PONV outcomes between RA containing enhanced recovery programs and nonregional anesthesia containing care pathways, 5 found the RA to have improved PONV, 1 found PONV to be higher in the RA group (total knee arthroplasty under spinal anesthesia versus TIVA with propofol and remifentanil[96]), and 12 found no difference.[97]

Propofol TIVA. An SRMA of RCTs showed that the PONV risk with propofol TIVA is comparable to volatile anesthesia plus single-agent prophylaxis (5-hydroxytryptamine 3 [5-HT_3] receptor antagonists and droperidol; evidence A1).[71] When used in combination with other prophylactic agents, propofol TIVA further reduces the risk of PONV (evidence A2).[98,99] Subhypnotic doses of propofol infusion, in combination with an antiemetic, also significantly reduced the incidence of PONV (evidence A2).[100,101]

Supplemental Oxygen. An SRMA of RCTs showed that supplemental oxygen was not associated with significant change in the overall risk of PONV, but the risk of early vomiting in abdominal surgery was lower.[42]

Novel Interventions. Since the last iteration of the guideline, a new Cochrane SRMA identified 6 studies comparing the risk of PONV in patients, who had neuromuscular junction blockade reversed with sugammadex compared to neostigmine, and reported that the PONV risk is lower with sugammadex (NNT = 16).[75] The quality of evidence was limited, however, due to inclusion of open-label studies as well as risk of bias due to unclear baseline PONV risk of the participants.

Weibel et al[102] conducted an SRMA on the use of IV lidocaine and PONV and reported that in laparoscopic abdominal procedures, the PONV risk is lower with lidocaine infusion. No benefit was seen with other surgery types.[103]

Baseline Risk Reduction in Children. New literature in the pediatric population confirms the well-established adult data in regard to TIVA (evidence A1), liberal fluid therapy (evidence A3), and opioid-sparing techniques (evidence A1) in reducing baseline risk for POV/PONV in children.[104–109] Opioid-sparing techniques remain a mainstay in reducing baseline risk for POV/PONV. RA, most commonly caudal blocks with or without systemic dexamethasone under GA have previously been reported as safe and effective at reducing pain, opioid requirements, and rates of emesis in children.[110] The panel believes that other regional analgesia techniques, such as TAP blocks, may also help in reducing opioid requirements. In settings where regional blocks are contraindicated or not available, systemic non-opioid analgesia may be viable alternatives.

IV lidocaine has been reported to reduce the risk of POV in a double-blinded RCT of 92 children undergoing tonsillectomy. Children receiving a 1.5 mg/kg lidocaine bolus followed by a 2 mg/kg/h lidocaine infusion were 62% less likely to have POV compared to children with saline infusion (P = .024).[107]

Two studies assessed α_2 agonists and their influence on PONV. An SRMA, while statistically heterogeneous, found reduced rates of PONV as a secondary outcome in children receiving intranasal dexmedetomidine for separation anxiety when compared to intranasal or oral midazolam (evidence A1).[111] In a randomized double-blinded study, the oral clonidine group had significantly less episodes of PONV and need for rescue antiemetics compared to the placebo group.[108] Further evidence is needed in children, but α_2 agonists warrant consideration in multimodal regimens aimed at reducing PONV risk in children.

Two studies compared perioperative IV acetaminophen (15 mg/kg) to saline and found a significantly reduced risk of PONV in the acetaminophen group. One of the studies analyzed 96 children and found that the incidence of POV during the first 6 hours postoperatively was significantly lower in the preoperative acetaminophen group than in the placebo and postoperative acetaminophen groups (P < .001).[106] The other study reviewed had 90 children undergoing strabismus surgery and found that rates of PONV were significantly lower in the dexamethasone and acetaminophen groups compared to dexamethasone only group[112] (evidence A2).

Liberal fluid therapy remains a well-established intervention for reducing baseline risk of POV as previously stated in multiple studies from the 2014 guidelines. Further evidence from a single RCT involving 150 children supports our recommendations of liberal therapy with lactated ringer's (30 vs 10 mL/kg) being effective at reducing PONV.[109]

Guideline 3. Administer PONV Prophylaxis Using 2 Interventions in Adults at Risk for PONV

In this iteration of the PONV guideline, one of the major changes is that we now recommend the use of multimodal prophylaxis in patients with one or more risk factors. This decision was made due to the concern

Table 4. Antiemetic Doses and Timing for Prevention of PONV in Adults

Drugs	Dose	Evidence	Timing	Evidence
Amisulpride	5 mg	A2[113,114]	At induction	A2[113,114]
Aprepitant	40 mg PO	A1[115–117]	At induction	A2[118]
Casopitant	150 mg PO	A1[119–121]	At induction	
Dexamethasone	4–8 mg IV	A1[122]	At induction	A1[123]
Dimenhydrinate	1 mg/kg IV	A1[124–126]		
Dolasetron	12.5 mg IV	A2[127–129]	End of surgery; timing may not affect efficacy	A2[128]
Droperidol[a]	0.625 mg IV	A1[130,131]	End of surgery	A1[132]
Ephedrine	0.5 mg/kg IM	A2[133,134]		
Granisetron	0.35–3 mg IV	A1[135,136]	End of surgery	A1[137–139]
Haloperidol	0.5 to <2 mg IM/IV	A1[140]		
Methylprednisolone	40 mg IV	A2[141]		
Metoclopramide	10 mg	A1[142]		
Ondansetron	4 mg IV 8 mg PO or ODT	A1[143,144]	End of surgery	A1[145]
Palonosetron	0.075 mg IV	A1[146–148]		
Perphenazine	5 mg IV	A1[149]		
Promethazine[a]	6.25 mg	A2[150,151]		
Ramosetron	0.3 mg IV	A1[152]	End of surgery	A2[152]
Rolapitant	70–200 mg PO	A3[153]	At induction	
Scopolamine	Transdermal patch	A1[154,155]	Prior evening or 2 h before surgery	A1[156]
Tropisetron	2 mg IV	A1[157]	End of surgery	

These recommendations are evidence-based and not all the drugs have an FDA indication for PONV. Drugs are listed alphabetically.
Abbreviations: FDA, Food and Drug Administration; IM, intramuscular; IV, intravenous(ly); ODT, orally disintegrated tablet; PO, per os; PONV, postoperative nausea and vomiting.
[a]See FDA Black box warning.

Table 5. Pharmacologic Combination Therapy for Adults and Children

Adults
5-HT_3 receptor antagonists + dexamethasone
Ondansetron: (A1)[158,159]
Palonosetron: (A2)[160–164]
Ramosetron: (A2)[165,166]
Granisetron: (A3)[167]
Tropisetron: (A3)[168]; with methylprednisolone (A3)[169]
5-HT_3 receptor antagonists + aprepitant
Ondansetron: (A2)[170,171]
Ramosetron: (A3)[172]
Palonosetron: (A3)[173]
Aprepitant + dexamethasone: (A2)[174,175]
5-HT_3 + droperidol
Ondansetron + droperidol: (A3)[176]
Granisetron + droperidol: (A3)[177]
Palonosetron + droperidol: (A3)[178]
Other 5-HT_3 combination therapies:
Ondansetron + haloperidol: (A3)[179]
Haloperidol + dexamethasone + ondansetron: (A3)[180]
Ondansetron + betahistine: (A2)[181,182]
Ramosetron + gabapentin: (A3)[183]
Midazolam + ramosetron: (A3)[184]
Other antidopaminergic combination therapies
Dexamethasone + haloperidol: (A2)[185,186]
Metoclopramide + dimenhydrinate: (A3)[187]
Amisulpride +1 nondopaminergic antiemetic: (A3)[188]
Haloperidol + midazolam: (A2)[189,190]
Acupoint stimulation + pharmacoprophylaxis: (A2)[191,192]
Others
Propofol + dexamethasone: (A3)[193]
Dexamethasone + dimenhydrinate:[194] (A3)
Gabapentin + dexamethasone: (A3)[195]
Children
Ondansetron + dexamethasone: (A1)[196]
Ondansetron + droperidol (A3)[197]
Tropisetron + dexamethasone (A3)[198]

Abbreviation: 5-HT_3, 5-hydroxytryptamine 3.

over inadequate prophylaxis as well as the availability of antiemetic safety data. The dosages and timing of antiemetics for adult PONV prophylaxis are summarized in Table 4; examples of combination therapies for PONV prophylaxis are summarized in Table 5. A summary of the proposed adult PONV guideline is presented in infographic format in Figure 6.

5-HT_3 Receptor Antagonists.

Ondansetron. Ondansetron is the most commonly used and studied 5-HT_3 receptor antagonist and is considered the "gold standard" in PONV management (evidence A1).[199] It has comparable antivomiting and antinausea effects when used as a single or combination medication for prophylaxis or treatment at a 4 mg IV dose or 8 mg oral disintegrating tablet with a 50% bioavailability.[200] The NNT is 6 for prevention of vomiting and 7 for nausea. The number needed to harm (NNH) is 36 for headache, 31 for elevated liver enzymes, and 23 for constipation.[143] Ondansetron has similar effectiveness compared to dexamethasone 4–8 mg[201] and haloperidol.[202] Ondansetron is less efficacious than ramosetron 0.3 mg IV,[144,203,204] granisetron 1–3 mg,[205] palonosetron 0.075 mg,[206–208] aprepitant 80 mg orally,[115] and fosaprepitant 150 mg IV.[209] Ondansetron is more efficacious than metoclopramide 10 mg IV[210] and dexmedetomidine.[211]

Dolasetron. Dolasetron is a highly specific and selective 5-HT_3 receptor antagonist indicated for prevention and treatment of PONV (evidence A2). It has low affinity for dopamine receptors. A prophylactic IV dose for

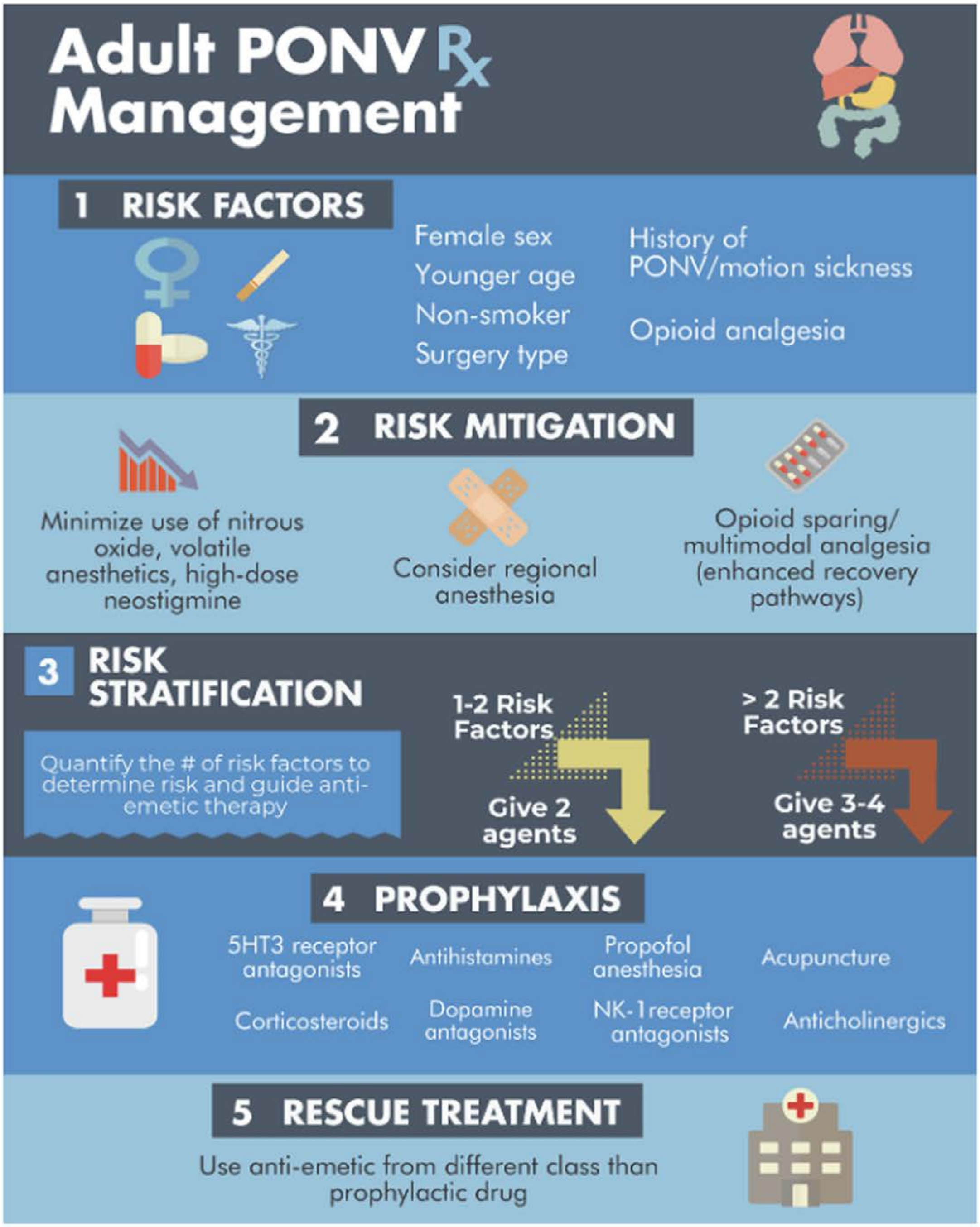

Figure 6. Algorithm for PONV management in adults. Summary of recommendations for PONV management in adults, including risk identification, stratified prophylaxis, and treatment of established postoperative nausea and vomiting. Note that 2 antiemetics are now recommended for PONV prophylaxis in patients with 1–2 risk factors. 5-HT_3 indicates 5-hydroxytryptamine 3; PONV, postoperative nausea and vomiting. The Figure reused with permission from the American Society for Enhanced Recovery. For permission requests, contact info@aserhq.org.

adults of 12.5 mg IV administered 15 minutes before the end of anesthesia has similar efficacy to 4 mg ondansetron.[127–129] Dolasetron is no longer marketed in the USA due to the concerns over QT prolongation.[212] There are no changes from the previous guidelines.

Granisetron. Granisetron 0.35–3 mg (5–20 µg/kg) IV has similar PONV efficacy compared to other first-generation 5-HT_3 receptor antagonists and to dexamethasone 8 mg[135] (evidence A1). One study showed that granisetron 0.3 mg IV had better effectiveness than ondansetron 4 mg IV.[136] In patients undergoing middle ear surgery, granisetron resulted in less PONV than ondansetron up to 24 hours postoperatively.[136] In patients undergoing laparoscopic cholecystectomy, granisetron was comparable to palonosetron in the first 24 hours postoperatively, but less efficacious in 24–48 hours postoperatively.[213] There are no new changes to report since the 2014 guidelines.

Tropisetron. Tropisetron is a competitive and selective 5-HT3 receptor antagonist and has antinausea and antiemetic properties used mostly for chemotherapy-induced nausea and vomiting (CINV). While not approved in the United States, it is used in Europe and Asia. NNT for prevention of nausea is 6.7 and 5 for vomiting (evidence A1).[157] The manufacturer's recommended dosing for tropisetron is 2 mg IV; however doses of up to 10 mg IV have been used in clinical trials.[157] Tropisetron 5 mg IV before the start of anesthesia has been found effective for PONV prevention for breast and gynecologic surgery.[214] Larger doses appear to have a longer clinical duration.[215] There are no changes from the previous guidelines.

Ramosetron. Ramosetron is a second-generation 5-HT_3 receptor antagonist licensed in Japan and Southeast Asia and approved for the treatment of nausea, vomiting, and diarrhea-predominant irritable bowel syndrome in males. The most effective adult dose and route of administration for PONV prevention and treatment is 0.3 mg IV.[152] Side effects include drowsiness, dizziness, muscle pain, sedation, constipation, and diarrhea. For PONV prevention, ramosetron 0.3 mg was more effective than ondansetron 4 mg[216] (evidence A1). When added to a PCA opioid infusion, ramosetron 0.3 mg was more effective than placebo, dexamethasone 10 mg, or palonosetron 0.075 mg.[217] For PONV treatment, ramosetron 0.3 mg has similar effectiveness as ondansetron 4 mg.[218]

Palonosetron. As a second-generation 5-HT_3 receptor antagonist, palonosetron has a 40-hour half-life, allosteric binding, positive cooperativity, receptor internalization, and 5-HT_3/neurokinin 1 (NK1) receptor inhibition.[219,220] In several meta-analysis studies[146–148] of PONV prevention, palonosetron 0.075 mg was more effective than ondansetron 4 and 8 mg, granisetron 1 mg, dexamethasone 5 and 8 mg, dolasetron 12.5 mg, tropisetron 2 mg, and ramosetron 0.3 mg (evidence A1). Palonosetron has similar effectiveness to aprepitant 40 mg per os (PO).[116] Palonosetron combined with sevoflurane/N_2O anesthesia reduced the incidence of PONV as much as a total TIVA technique.[221] Combining palonosetron with TIVA reduced PONV more than TIVA alone.[222] Combined with palonosetron 0.075 mg prophylaxis, those receiving palonosetron 0.075 mg added to a PCA infusion had less PONV than those receiving palonosetron prophylaxis alone.[223]

NK1 Receptor Antagonists.

Aprepitant. Aprepitant is a NK1 receptor antagonist with a half-life of 40 hours, available in oral and parenteral (fosaprepitant) forms (evidence A1).[3] All dosages (40, 80, and 125 mg) have been shown more effective in reducing the incidence of POV rather than nausea. Aprepitant 40 mg orally has the same PONV prevention effect as palonosetron 0.075 mg IV.[116] Aprepitant 40 and 80 mg orally is more efficacious than ondansetron.[115,224] Fosaprepitant (a prodrug of aprepitant) 150 mg IV is more efficacious than ondansetron.[209,225–227] In a meta-analysis which compared aprepitant to various other antiemetics and placebo, aprepitant reduced the incidence of vomiting on both POD 1 and 2; however, the quality of evidence was limited by the significant heterogeneity in the results.[117] In addition, provisional data from a Cochrane network meta-analysis by Weibel et al[102] suggest that NK1 receptor antagonist monotherapy has similar efficacy to several combination therapies.

NK1 receptor antagonists may be useful prophylactic antiemetics when postoperative emesis is highly undesirable, such as in gastric and neurosurgery. Further study is needed on the effect of NK1 receptor antagonists on opioid requirements.

Casopitant. Casopitant has been shown to be more effective to reduce POV than nausea (evidence A1).[119–121] The use of NK1 receptor antagonists could delay the time to first vomiting episode compared with ondansetron. Casopitant has not been approved for PONV use.

Rolapitant. Rolapitant is a long-acting, NK1 receptor antagonist which may be effective in PDNV because of its half-life of 180 hours. While there was no difference between rolapitant 70 and 200 mg orally and ondansetron 4 mg IV at 24 hours, fewer study patients had emesis at 72 and 120 hours (evidence A3).[153] Rolapitant has not been approved for PONV use.

Vestipitant. Six doses (4–36 mg) of vestipitant were compared with ondansetron 4 mg for treatment of breakthrough PONV after failed ondansetron prophylaxis. Although the overall efficacy was noninferior between vestipitant and ondansetron, vestipitant had a lower rate of emesis, suggesting that vestipitant may possibly be useful for PONV similar to other NK1 receptor antagonists (evidence A3).[228]

Corticosteroids.

Dexamethasone. Perioperative glucocorticoids have been used for many years to reduce the incidence of PONV. Currently, the recommended dose of dexamethasone ranges between 4 and 10 mg. There has been an increase in the number of studies evaluating the use of 8 mg (0.01 mg/kg) of dexamethasone or higher doses with positive results (evidence A1).[229–231] In general, there are limited data for trials using doses higher than 8 mg. A meta-analysis of trials using dexamethasone for PONV prophylaxis found no difference in antiemetic efficacy between the 4 and 5 mg vs the 8 and 10 mg dose of dexamethasone.[122] Additionally, with reference to timing, the data support the early dosing of dexamethasone at the beginning of a case rather than at the end for the prevention of PONV.[232] Dexamethasone prophylaxis resulted in comparable incidence of PONV compared to 5-HT_3 receptor antagonists (primarily ondansetron).[122] One exception to the equivalence between dexamethasone and 5-HT_3 receptor antagonists may be palonosetron, which at a dose of 75 μg showed superiority over dexamethasone 8 mg for overall PONV reduction in the 0–24 interval.[233,234]

Additionally, as an added advantage over 5-HT_3 receptor antagonists, dexamethasone reduced the need for analgesics in many studies,[235,236] including cases with neuraxial anesthesia.[237] A meta-analysis suggested that the opioid-sparing effects associated with dexamethasone use in PONV do not appear to be dose-dependent, but evidence is conflicting.[238] Dexamethasone also improves respiratory parameters,[239] reduces fatigue, provides a better quality of recovery,[240] and reduces the LOS in hospital.[241]

The question of safety, as it relates to dexamethasone, has been raised in numerous studies. It appears that dexamethasone, especially given in a single dose, has few adverse effects. A recent Cochrane Database analysis of 37 trials concluded that dexamethasone does not appear to increase the risk for postoperative infections, but with wide confidence interval. Additionally, the included studies excluded patients at risk for delayed wound healing, making extrapolation to larger populations difficult.[242] There is even a possible suggestion that dexamethasone decreases the incidence of infectious complications in patients undergoing pancreaticoduodenectomy.[243] An additional review of 56 trials indicated that corticosteroids, primarily dexamethasone did not increase wound infection rates, anastomotic leak, wound healing, bleeding, or clinically significant hyperglycemia.[244] Dexamethasone appears to induce only a mild blood glucose elevation in patients.[245] Even in the presence of diabetes, there is minimal evidence to support a clinically significant increase in blood glucose levels with less elevations reported with the 4 mg compared with higher dose.[242,244,246,247] Higher doses of dexamethasone, above those typically used for PONV, appear to have a more significant effect on glucose levels.[248] The risk of increased bleeding with the use of dexamethasone has been raised.[249] Based on the limited number of available studies, dexamethasone does not appear to significantly increase the risk of postoperative bleeding, even in tonsillectomy patients.[250] Finally, the association of steroids and the possibility of cancer recurrence has been addressed in at least 2 fairly recent studies, both in women, demonstrating no evidence for an increased risk with dexamethasone at doses of 4–10 mg.[251,252]

There is some evidence that prophylaxis with multiple doses of dexamethasone is more effective than single intraoperative dose.[253,254] Interval dosing under anesthesia may be possible in very long surgical procedures. However, it is unclear if repeated doses may increase the risk of corticosteroid-related complications (such as infection, bleeding, and hyperglycemia).

Other Corticosteroids. Other corticosteroids appear to have similar efficacy to dexamethasone in terms of a reduction of PONV and analgesic effects.[255] A recent meta-analysis reported that perioperative steroids in knee arthroplasty significantly reduce postoperative pain.[256] Both low (40 mg) and high (125 mg) doses of methylprednisolone have been shown to be effective in reducing PONV.[255,257] In a meta-analysis of hip and knee arthroplasty patients, methylprednisolone, in doses ranging from 40 to 125 mg, was shown to reduce pain and PONV (evidence A1).[141] Not all steroids appear to have the same relative efficacy toward PONV prevention. In a trial using betamethasone 8 mg in patients undergoing elective breast cancer surgery, there was only a small effect in reducing PONV compared to placebo.[258]

Antidopaminergics.

Amisulpride. Amisulpride is a dopamine D_2, D_3 receptors antagonist. It is an oral antipsychotic (at a dose of 50–1200 mg/d).[259] An IV formulation was recently approved for the management of PONV. Amisulpride 5 mg is more effective than placebo in achieving complete response and reduction in nausea severity (evidence A2),[113,114] while doses of 1 and 20 mg are not effective (evidence A3).[113] When used for the treatment of established PONV, amisulpride 5 and 10 mg is more effective than placebo in patients who received no prior prophylaxis (evidence A3).[188] However, in patients who received prior PONV prophylaxis with nonantidopaminergic agents, amisulpride 10 mg but not 5 mg was more effective than placebo for the treatment of established PONV (evidence A3).[260] Administration of amisulpride is associated with mild increase in prolactin level, the clinical significance of which is unclear. Studies have reported that antiemetic dose of amisulpride was not associated with sedation, extrapyramidal side effect, or QTc prolongation.[113,114,188,260–262]

Droperidol. Droperidol is effective for the prophylaxis of PONV in doses of 0.625–1.25 mg (evidence A1).[130,132] It is recommended to be administered at the end of surgery to optimize antiemetic efficacy in the postoperative period (evidence A1).[132] While droperidol was used as a first-line agent for PONV prophylaxis, its use has significantly declined in many countries following a Food and Drug Administration (FDA) black box warning in 2001, which imposed restrictions on the use of droperidol due to the risk of sudden cardiac death when used in doses >25 mg.[263] Several studies have however suggested that antiemetic doses of droperidol are safe, are associated with only a transient prolongation in QTc comparable to that of ondansetron, and are not associated with changes in transmural dispersion of repolarization.[264,265] The QT prolongation induced by the combination of ondansetron and droperidol is not different from that induced by each drug alone.[266] A large retrospective study involving 20,122 patients who received droperidol 0.625 mg for PONV prophylaxis also found no increase in the risk of polymorphic ventricular tachycardia.[267] A recent study found no statistically significant difference in the risk of akathisia between ondansetron 4 mg (0.8%), droperidol 0.625 mg (1.2%), and droperidol 1.25 mg (3.4%).[268] A meta-analysis confirmed that low doses of droperidol <1 mg are effective,[269] and given that adverse effects might be dose related, a dose of 0.625 mg is recommended by the panel.

Haloperidol. The use of haloperidol as an antiemetic is not FDA approved, but interest in its use in PONV increased following the FDA black box warning on droperidol.[270] Low doses of 0.5–2 mg are effective for PONV prophylaxis with efficacy and side effects, including QT prolongation, not different from those of 5-HT_3 receptor antagonists (evidence A1).[140,271] When given after induction of anesthesia, the efficacy and side-effect profile of haloperidol 1 mg was also not different from droperidol 0.625 mg with no extrapyramidal side effects reported in either group.[272] Haloperidol 2 mg administered at induction of anesthesia or at the end of surgery did not affect the risk of PONV over 24 hours.[273] When used for the treatment of established PONV in PACU, haloperidol 1 mg was not inferior to ondansetron 4 mg in the proportion of PONV-free patients at 4 and 24 hours after administration but was associated with increased sedation.[202]

Metoclopramide. The antiemetic efficacy of a 10 mg dose of metoclopramide is uncertain. An earlier meta-analysis concluded that this dose has no clinically relevant antiemetic effect.[274] However, this meta-analysis included studies by Fujii et al, which were later found to be fabricated.[275] A more recent meta-analysis[142] excluding the retracted studies by this group concluded that a 10 mg dose of metoclopramide may be effective for the prevention of PONV with an NNT of 8–10 (evidence A1). Metoclopramide was, however, not effective when used in combination with other antiemetics based on limited numbers of available studies. A large study involving 3140 patients who received PONV prophylaxis with 8 mg dexamethasone, randomized patients to placebo, metoclopramide 10, 25, or 50 mg. Only the 25 and 50 mg doses significantly reduced PONV (NNT 16.9 and 11.6, respectively).[34] Extrapyramidal symptoms were rare but were significantly higher in the 25 and 50 mg groups (0.8%) compared with the 10 mg metoclopramide group (0.4%). Metoclopramide may be useful in institutions where other dopamine antagonists are not available, but otherwise may not be very efficacious.

Perphenazine. Perphenazine is an atypical antipsychotic and a dopamine receptor antagonist. Limited data suggest that perphenazine is effective for the prophylaxis of PONV without increase in drowsiness or sedation, with the recommended dose being 5 mg IV (evidence A1).[149]

Antihistamine. A meta-analysis of trials comparing dimenhydrinate to placebo suggested that it was effective for PONV prophylaxis with an NNT of 8 and 5 for the early and late postoperative period, respectively (evidence A1). The optimal dosing, timing, and side-effect profile when used for the management of PONV are however unclear.[124]

A recent study investigated the impact of 2 doses of diphenhydramine (25 and 50 mg) on quality of recovery following outpatient laparoscopic gynecologic surgery. Only the 50 mg dose reduced the risk of PONV compared with placebo, but the quality of recovery was not different between the diphenhydramine and placebo groups (evidence A3).[276]

Data examining the use of promethazine for PONV prophylaxis are limited. When given at induction of anesthesia, promethazine 25 mg alone or 12.5 mg combined with ondansetron 2 mg were effective in reducing PONV at 24 hours following middle ear surgery.[150] The combination of promethazine 6.25 mg with granisetron 0.1 mg given at the end of surgery, followed by oral promethazine 12.5 mg and granisetron 1 mg given every 12 hours for 3 days, was more effective than promethazine alone in reducing the risk of PONV and PDNV[151] (evidence A2). Promethazine is also effective for the treatment of established PONV, with doses as low as 6.25 mg being as effective as higher doses and associated with less sedation[277,278] (evidence A2). In 2006, the Institute of Safe Medication Practices (ISMP) issued a safety alert with regards to the administration of promethazine by injection; this is followed by an FDA issued black box warning in 2009. The warning indicated a risk that the drug can leach out from the vein during IV administration and cause serious damage to the surrounding tissue. In addition, injecting promethazine in an artery or under the skin can cause severe tissue damage including gangrene. As a result of these risks, the FDA stated that deep intramuscular administration is the preferred route of administration. The warning also states that if IV administration is chosen, a properly functioning IV line should be ensured, and infusion should be given in a concentration no greater than 25 mg/mL and at a rate not to exceed 25 mg/min.[279,280]

Anticholinergics. Transdermal scopolamine is effective for PONV prophylaxis in PACU and for 24 hours postoperatively, with NNT = 6. Onset of effect is 2–4 hours, and can be applied presurgery or the night before. Adverse events are generally mild, most commonly visual disturbances, dry mouth, and dizziness (evidence A1).[154,155]

Other Antiemetics.

Gabapentinoids-Gabapentin and Pregabalin. Given 1–2 hours before surgery, gabapentin 600–800 mg orally has been shown to decrease PONV (evidence A1).[281–283] In laparoscopic cholecystectomy, gabapentin reduced pain severity, total morphine consumption, and PONV (25.2% vs 47.6%). Nausea and vomiting decreased as gabapentin dosage increased.[282,284] Preoperative gabapentin in patients undergoing abdominal surgery reduced PONV.[285] Disadvantages of γ-aminobutyric acid (GABA) analogs include sedation, visual disturbances, dizziness, and headache. Gabapentin was associated with respiratory depression in patients undergoing laparoscopic surgery.[282] In 2019, FDA released a drug safety communication warning against the risk of respiratory depression when gabapentinoids are used in combination with central nervous system (CNS) depressants such as opioids; when used as a part of the multimodal analgesic regimens, intraoperative opioids should be reduced and increased vigilance for may be warranted, especially in elderly patients.[286]

Midazolam. Meta-analysis showed a reduction in PON, POV, and PONV relative to controls after midazolam administration at induction (evidence A1).[287] There was no significant difference in PONV between midazolam and ondansetron given 30 minutes before the end of surgery. However, this is not recommended due to the possibility of sedation-related adverse events. Midazolam combined with other antiemetics had increased efficacy over single-agent therapy. Lower and higher dose midazolam showed no difference in PONV efficacy for prophylaxis efficacy.[288] The incidence of PONV was significantly reduced after administration at the end of surgery.[289] Midazolam 2 mg given 30 minutes before the end of surgery decreased PONV and was as effective as ondansetron 4 mg.[290] Limited data suggest that midazolam has similar efficacy to ondansetron in treating established PONV.[291]

Ephedrine. Ephedrine 0.5 mg/kg IM given near end surgery significantly reduces PONV for 3 hours postoperatively. Antiemetic effect and need for rescue are comparable to droperidol 0.04 mg/kg IM. Sedation during ambulatory surgery recovery is significantly less than placebo. Changes in mean arterial blood pressure (BP) and heart rate (HR) were not significantly different from placebo; caution should be observed with patients at risk for coronary ischemia (evidence A2).[292,293]

Nonpharmacologic Prophylaxis.

Pericardium 6 Acupuncture Point (PC6) Stimulation. An updated Cochrane review including 59 trials with 7667 subjects reported that PC6 stimulation was associated with a significant reduction in the risk of nausea, vomiting, and the need for rescue antiemetics compared with sham treatment (evidence A1).[294] The review also included a comparison of PC6 acupoint stimulation with 6 different types of antiemetic drugs (metoclopramide, cyclizine, prochlorperazine, droperidol, ondansetron, and dexamethasone), and found no difference in nausea, vomiting, or need for rescue antiemetics between PC6 stimulation and pharmacoprophylaxis. Trial sequential analyses suggested that further sham-controlled trials or RCT versus antiemetics are unlikely to change the conclusion. On the other hand, the evidence regarding the comparison of the combination of PC6 stimulation with antiemetic drugs compared to antiemetic drugs alone was of very low quality and inconclusive. The combination was more effective than antiemetic drugs alone for reducing vomiting and need for rescue antiemetics, but not nausea (evidence A1).[294] Acupoint stimulation was effective in reducing PONV regardless of whether stimulation was initiated before or after induction in anesthesia.[295] Monitoring of neuromuscular function with stimulation applied intraoperatively over the median nerve is effective in reducing the incidence of early PONV, especially with the use of tetanic stimulation.[296,297]

In addition to PC6, stimulation of other acupoints has also been used for PONV prophylaxis. One RCT in 2014 reported that stimulation of both the PC6 and L14 acupoints resulted in significantly lower incidence of PONV compared to PC6 alone (69.6% vs 85.7%; $P < .05$).[298] Another RCT reported that bilateral acupuncture at the ST36 acupoint was associated with significantly lower risk of PONV.[299]

Fluids. Adequate hydration is an effective strategy for reducing the risk of PONV. This can be achieved by minimizing perioperative fasting time, or using supplemental IV fluid to maintain clinical euvolemia. A recent Cochrane review showed that supplemental crystalloids (10–30 mL/kg) reduce the risk of both early and late PONV as well as the need for rescue antiemetics (evidence A1).[73] There is no difference between crystalloids and colloids infusion on the risk of PONV or need for rescue antiemetics when comparable volumes are used. However, a systematic review reported that colloids were more effective in reducing the risk of PONV in surgeries lasting >3 hours, but not in those lasting <3 hours (evidence A1).[74] Dextrose solutions infused intraoperatively or postoperatively were not found to be effective in reducing the risk of PONV (evidence A1).[300]

Carbohydrate Loading. Administration of a preoperative carbohydrate drink is included in many of the ERPs. Studies investigating the impact of carbohydrate drink on PONV have reported inconsistent results, but overall, the evidence suggests that it has no impact on the incidence of PONV (evidence A1).[301]

Aromatherapy. A recent Cochrane review evaluated the use of aromatherapy for the treatment of PONV, and found that, overall, aromatherapy did not reduce the incidence or severity of nausea, but reduced the need for rescue antiemetics. However, the level of evidence was low. When investigating different types of aromatherapy, the review found that peppermint aromatherapy was no more effective than placebo in reducing nausea severity at 5 minutes, but isopropyl alcohol aromatherapy resulted in shorter time to 50% reduction in nausea severity, less need for rescue antiemetics, but no difference in patient satisfaction. On the other hand, isopropyl alcohol vapor inhalation did not reduce the need for rescue antiemetics (evidence A1).[302]

Ginger. A meta-analysis investigating the efficacy of ginger for PONV prophylaxis reported no reduction in the incidence of PONV, but a small reduction in nausea scores. A subgroup analysis according to dose suggested a trend for better outcomes with higher doses of 1000 mg ginger compared to lower doses, but differences were not statistically significant, so more data are needed (evidence A1).[303]

Supplemental Oxygen. A meta-analysis found that high inspired oxygen concentration was not found to reduce the incidence of the composite outcome of PONV, but had a weak effect on late nausea. In patients who received inhalation anesthetics and no prophylactic antiemetics, high inspired oxygen concentration reduced both late nausea and vomiting, but the effect was modest (evidence A1).[304]

Chewing Gum. Chewing gum is showing promise for the treatment of PONV, with 1 small pilot study suggesting that chewing gum was not inferior to ondansetron for the treatment of PONV in female patients who underwent laparoscopic or breast surgery under GA (evidence A3).[305]

Others. Suggestive techniques (evidence A1),[306] healing touch (evidence A3),[307] and music (evidence A3)[308] were not found to be effective prophylactic modalities for PONV. *Morinda citrifolia* Linn (Noni fruit) was found to be effective in reducing the incidence of early nausea when used in a dose of 600 mg (evidence A3).[309] Administration of a low-dose naloxone infusion reduces postoperative nausea and the need for rescue antiemetics (evidence A1).[310]

Combination Therapies. In the review of studies on combination therapy in adults since the last Consensus Guideline, the panel determined that the recommendation remains unchanged. The panel found supporting evidence for the existing guideline and continues to recommend combination antiemetic therapy for patients at higher risk for PONV. The literature on combination of 2 or more antiemetics for prevention of PONV is robust and shows superiority over single agents for the majority of studies (evidence A1).[158–163,165,166,168–170,172,174,176,177,180–187,189,190,195,261,311–320] The use of combination therapy for prevention of PONV in adults is firmly established in current anesthesia practice.

New antiemetic combination therapies have been reported. These include palonosetron 0.075 mg and dexamethasone 4 or 8 mg.[159,234,321–324] This regimen was studied in several recent trials, with conflicting results. Bala et al[160] and Cho et al[161] found that palonosetron combined with 8 mg dexamethasone achieved significance for complete response or lower incidence of PONV over palonosetron alone while other studies reported no significant difference compared to palonosetron alone.[178,234,321,322,325] However, additional studies did show palonosetron in combination with other agents was efficacious.[160–164] Most notably, palonosetron plus dexamethasone had lower PONV than ondansetron plus dexamethasone (evidence A3),[326] and palonosetron plus aprepitant had lower PONV than ramosetron plus aprepitant (evidence A3).[173] Although the evidence is mixed on palonosetron alone versus palonosetron in combination, further research is needed with palonosetron in combination with other agents for prophylactic therapy.

The 5-HT_3 receptor antagonists are commonly used alone or in combination with dexamethasone 4 or 8 mg, and form the cornerstone of antiemetic prophylaxis for surgery (evidence A1). In a 2016 meta-analysis, 17 RCTs were assessed with 1402 study participants on combinations of 5-HT_3 receptor antagonists and dexamethasone. The results were that the combination therapy resulted in significantly reduced risk of PONV and lower rescue antiemetic requirement compared to 5-HT_3 receptor antagonists alone. In the subgroup analyses of individual 5-HT_3 receptor antagonists, dexamethasone in combination with ondansetron and palonosetron significantly reduced 24-hour PONV compared to 5-HT_3 receptor antagonists alone; the authors noted the data were insufficient for ramosetron and granisetron to reach a conclusion.[159]

Granisetron and tropisetron combinations were less frequently studied (evidence A2) and none of the evaluated studies included dolasetron as an agent for combination.[167–169,177] This is likely due to removal of dolasetron's different product presentations from the market in certain countries centered on concern for risk of developing arrhythmia. In a 2017 study of 1350 large and small bowel patients, the authors found the addition of a single dose of 8 mg dexamethasone combined with a routine antiemetic (most commonly ondansetron) significantly reduced the incidence of PONV at 24 hours and the need for rescue antiemetics for up to 72 hours with no increase in adverse events.[327]

The previous guidelines concluded that aprepitant 40 mg in combination with dexamethasone was superior to ondansetron with dexamethasone in preventing vomiting in neurosurgical patients.[3] Two studies have reported that aprepitant plus ondansetron is significantly more efficacious than ondansetron alone (evidence A2).[170,171] Aprepitant 40 mg orally in combination with dexamethasone is more efficacious than ondansetron with dexamethasone.[328] In a recent study comparing aprepitant alone to aprepitant plus scopolamine patch, there was no difference in complete response between the groups.[329] Many of the studies used higher doses of aprepitant (80 vs 40 mg) which was not as common in the 2014 guidelines.[172,174,175,318]

Antihistamines exhibit antiemetic benefit but are used less frequently than others in combination therapies, due to concern of possible sedation. Betahistine is a strong H_3 receptor antagonist, and 2 studies compared betahistine plus ondansetron to ondansetron only for prophylaxis. Both reported significantly less PONV with the combination prophylaxis.[181,182] Kizilcik et al[194] compared dexamethasone 8 mg plus dimenhydrinate 1 mg/kg to dexamethasone 8 mg plus ondansetron 4 mg, and reported that dexamethasone plus dimenhydrinate was more effective.

Our review of the recent literature found limited number of combination studies that included droperidol.[176,177,330] Matsota et al[176] found droperidol plus ondansetron is more effective than either agent alone.

Several studies have reported that midazolam, when used in combination with antiemetic agents, further decreased PONV.[167,184,189,190,315,319,331] Grant conducted a meta-analysis of midazolam on PONV with a subgroup analysis of midazolam as part of combination therapy and showed increased efficacy over single-agent therapy alone (evidence A1). Grant determined it is likely that PONV can be prevented at subhypnotic doses (<0.05 mg/kg) without the many common side effects associated with higher dose midazolam.[288] Nevertheless, caution is advised in using midazolam for PONV.

In a clinical trial of 1147 patients, the combination of amisulpride with ondansetron or dexamethasone was more effective than ondansetron or dexamethasone alone in reducing PONV and rescue antiemetic requirement (evidence A3).[261]

Combination therapy research using more than 2 agents is emerging. Examples of triple agent combinations include aprepitant 80 mg + dexamethasone 4–8 mg + ondansetron 4 mg regimen was superior over the dual combination of dexamethasone + ondansetron in patients receiving TIVA combined with neuraxial blockade for elective laparoscopic surgery[175]; haloperidol 2 mg + dexamethasone 8 mg + ondansetron 8 mg which reduced PONV and need for rescue over a single agent but did not show improved efficacy over the 2 agent combination for all end points[180]; dexamethasone 8 mg + ondansetron 4 mg + droperidol 0.625 mg was compared to placebo and reduced PONV 0–6 hours.[332] More research is needed for investigating efficacy using 3 or more pharmacological agents prophylactically. Additionally, close monitoring should be considered for possible added risk of side effects with the use of multiple agents.

Although recent evidence continues to support the use of 2 or more antiemetics, there has not been sufficient evidence to guide the clinician to select the most effective individual antiemetic that provides the optimal combination over other combination therapies with the exception of using agents from a different pharmacologic class.[333] The selection of agents from a different pharmacological class is still recommended to cover different receptor sites to optimize the antiemetic effect. The exact mechanism is neither clearly established nor is it clear as to which receptor site(s) is/are triggered in a patient undergoing surgery and anesthesia. Both nausea and vomiting may be prompted through a variety of central and peripheral mechanisms. Additionally, the least effective optimal doses to be used in the antiemetic combination have not been clearly identified. The studies in the latest review have used a variable range of dosing strategies such as the use of weight-based dosing versus single standard dosing. In some studies, use of higher dosages than the FDA-approved dosing has often been used. The higher dosing found in the current studies are 8 vs 4 mg dexamethasone, 80 vs 40 mg aprepitant, 8 vs 4 mg ondansetron, 1.25 vs 0.625 mg droperidol, and 10 vs 5 mg tropisetron.[158,160–162,169,172,174,176,180,182,261,311–313,316–319]

Finally, several studies have reported the use of nonpharmacological interventions as part of the combination therapies. Chen et al[299] conducted a study of patients undergoing laparoscopic surgery receiving placebo, IV ondansetron, bilateral ST36 acupuncture, or both. Another study compared the use of (1) dexamethasone 4 mg IV, (2) acupuncture in the PC6 point, (3) combination of dexamethasone and acupuncture, and reported that the combination was associated with significantly lower incidence of PONV than either intervention alone.[191] White et al[192] compared the use of a disposable acupressure device or a sham device applied to PC6, in combination with 4 mg dexamethasone and 4 mg ondansetron, and found that addition of PC6 acupressure significantly reduced the risk of PONV up to 72 hours postoperatively (12% vs 30%; $P = .03$). Two recent meta-analyses regarding acupoint stimulation for PONV prophylaxis both concluded that the quality of evidence for the use of acupoint stimulation as a part of combination therapy is low due to study limitations and heterogeneity.[294,334]

Cost-Effectiveness. With rising health care costs, the cost-effectiveness of therapy should be considered in determining appropriateness of PONV prophylaxis. Proper pharmacoeconomic analysis can also assess the value of using 1 particular drug or drug combination compared to another, taking into consideration both the cost of drugs and patient care.[191,335] Many studies have evaluated the cost-effectiveness of different PONV prophylaxis therapies.[191,335–338] However, the majority of these studies are limited by variable methodologies, small sample size, and historically high drug costs as they were performed before the availability of generic antiemetics.[339,340] One point to consider in cost-effective analysis is that for every antiemetic intervention, the absolute risk reduction (ARR) and therefore NNT depends on the relative risk reduction (RRR), which represents the efficacy of the intervention, but also the control event rate (CER), which in this case is the incidence of PONV. As a result, the higher the baseline incidence of PONV, the lower the NNT would be for any antiemetic intervention. This supports the use of a risk stratification system in optimizing the cost-effectiveness of PONV prophylaxis.[25,341]

According to established guidelines, cost-effective analyses should be conducted from both the health care sector perspective and the societal perspective.[342–345] Willingness to pay is a reliable measure of the patient perspective in cost-benefit analyses.[346] Studies by Macario et al[346] and Gan et al[347] found that patients are willing to pay approximately $30 to prevent PONV, while Diez[348] found parents are willing to spend approximately $80 to prevent PONV in their children. On the other hand, Dzwonczyk et al[336] found that the average hospital cost and charge per antiemetic drug dose were $0.304 and $3.66, respectively. Thus, the average charge to the patient for 3 antiemetic doses was <$11. From a health care sector perspective, the authors found that the hospital's net profit increased linearly with increased PONV prophylaxis administration.[336]

Modifying the anesthetic regimen can be a cost-effective strategy.[349] A study by Elliott et al[350] showed that using propofol for induction and isoflurane for maintenance of GA was associated with the lowest cost per episode of PONV avoided than an induction/maintenance combination of either propofol/sevoflurane or sevoflurane/sevoflurane. However, given availability of generic sevoflurane, this cost analysis may show different results today. It may also prove cost-effective to reduce baseline risk through opioid minimization. Marrett et al[351] reported that patients receiving oral immediate-release opioids in outpatient setting had higher risk of hospitalization, emergency department, and clinic visits, as well as higher health care costs due to nausea and vomiting.[351]

High emetogenic surgeries are associated with longer PACU stays and costs.[337] It is estimated that each episode of emesis delays discharge from the PACU by approximately 20 minutes.[352] While it may appear significant from the patient's perspective, the impact from the health care cost perspective is uncertain. In a retrospective study of patients undergoing ambulatory surgery, Dexter and Tinker[353] showed that the length of PACU stay for all patients would only have been reduced by <5% if PONV had been eliminated in this patient population. Parra-Sanchez et al[338] performed a time-motion economic analysis of PONV in patients undergoing ambulatory surgery. The authors prospectively followed 100 ambulatory surgery patients from the time of surgery through the third postoperative morning. The authors found that patients who experienced PONV following ambulatory surgery, 60% of them experienced symptoms following discharge. On average, patients with PONV spent 1 hour longer in the PACU, required more nursing time, and incurred greater total cost. PONV was associated with an adjusted incremental total cost of $74. In bariatric surgery patients, PONV is one of the most common causes of unplanned readmission.[354] PONV does not seem to have a measurable impact on rate of unanticipated admission, physician visits, or time to return to normal activity[338,339] However, the development of PONV is associated with significantly lower postoperative quality of life[338] while high-risk patients demonstrate higher satisfaction with PONV prophylaxis.[355]

While there is extensive evidence that multimodal prophylaxis is clinically effective, the evidence on cost-effectiveness is limited. More cost-effectiveness analyses are needed on PONV management.

Guideline 4. Administer Prophylactic Antiemetic Therapy to Children at Increased Risk for POV/PONV; As in Adults, Use of Combination Therapy Is Most Effective

Based on the POV/PONV risk, there are specific recommendations for prophylaxis in children. Thus, when the risk is extremely low and the surgeries last <30 minutes, one may refrain from administering antiemetic prophylaxis. On the other hand, prophylaxis is recommended with increase in risk as suggested in Figure 4, with combination therapy for children considered high risk for POV/PONV. Intraoperative steroids in combination with 5-HT$_3$ receptor antagonists have the strongest evidence in children. Rescue drugs should be reserved only for those in whom prophylaxis has been only partially helpful. Antiemetic drugs and dosages for POV/PONV prophylaxis in children are summarized in Table 6.

Table 6. Antiemetic Doses for Prophylaxis of POV/PONV in Children

Drug	Dose	Evidence
Aprepitant	3 mg kg^{-1} up to 125 mg	A3[356]
Dexamethasone	150 μg kg^{-1} up to 5 mg	A1[196]
Dimenhydrinate	0.5 mg kg^{-1} up to 25 mg	A1[124]
Dolasetron	350 μg kg^{-1} up to 12.5 mg	A2[357]
Droperidol[a]	10–15 μg kg^{-1} up to 1.25 mg	A1[132]
Granisetron	40 μg kg^{-1} up to 0.6 mg	A2[358]
Ondansetron[b]	50–100 μg kg^{-1} up to 4 mg	A1[359]
Palonosetron	0.5–1.5 μg kg^{-1}	A2[360,361]
Tropisetron	0.1 mg kg^{-1} up to 2 mg	A1[157]

These recommendations are evidence-based and not all the drugs have an FDA indication for PONV. Drugs are listed alphabetically.

Abbreviations: FDA, Food and Drug Administration; PONV, postoperative nausea and vomiting; POV, postoperative vomiting.

[a]See FDA black box warning. Recommended doses 10–15 μg/kg.

[b]Approved for POV in pediatric patients aged ≥1 mo.

Propofol. There are now multiple systematic reviews that support the use of propofol TIVA as an effective intervention for reducing baseline risk of PONV in children undergoing strabismus surgery (evidence A1). A meta-analysis including 558 patients <18 years of age undergoing GA for strabismus surgery assessed the rates of POV with TIVA compared to single pharmacologic prophylaxis. The incidence of POV was similar among both groups.[104] A second meta-analysis of 762 children in 9 RCT's comparing propofol TIVA to no pharmacologic prophylaxis supported previous findings of reduced rates of emesis in the propofol group.[104] However, both reviews showed a significant risk of oculocardiac reflex and bradycardia requiring intervention in the TIVA groups (evidence A1).[104,362] The increased rates of oculocardiac reflex in propofol infusion groups have been previously reported in both the adult and pediatric populations and are presumed to be related to the parasympathomimetic effect of propofol.[105,363] The incidence of this reflex in children is likely more pronounced due to naturally higher vagal tone. While TIVA is an effective antiemetic intervention in children, the benefits of antiemetic prophylaxis with propofol TIVA need to be weighed with the increased risk of bradycardic events in this group. However, this risk may be overcome with glycopyrrolate that also reduces nausea and vomiting.

NK1 Receptor Antagonists. We identified one new dose-finding multicenter double-blinded RCT assessing the safety and efficacy of aprepitant in the pediatric population (evidence A3). Salman et al[356] randomized 220 children (ages birth–17 years) to 10, 40 (adult recommended dose), or 125 mg of aprepitant and 0.1 mg/kg IV ondansetron. The authors reported that complete and partial response rates were comparable between the 10, 40, 125 mg dosing groups, which were similar to that of the ondansetron group. There was also no significant difference between the 4 groups in terms of adverse events.[356]

5-HT$_3$ Receptor Antagonists. There has been a large body of literature previously reporting the safety and efficacy profiles of multiple 5-HT$_3$ receptor antagonists in the pediatric population with ondansetron being the most recognizable pharmacologic agent in this class (evidence A1).[364] Recent adult literature has suggested that palonosetron, a newer generation 5-HT$_3$ receptor antagonist may be more effective at reducing PONV due to its longer half-life than other common 5-HT$_3$ receptor antagonists. Two dose-finding studies with palonosetron have since been published in children. Two hundred eighty-six children undergoing GA for dental procedures were randomized to 4 different dosing regimens of 2.5, 5.0, 7.5 μg or placebo. Compared to the placebo group, PONV was significantly lower in all palonosetron doses with no intergroup variability in rates of PONV or adverse drug events. A single 2.5 μg IV dose of palonosetron warrants further evaluation and efficacy comparisons to ondansetron and combination therapy regimens.[360] A second study randomized 150 children into palonosetron dosing regimens of 0.5, 1.0, 1.5 μg/kg and found significant reductions in PONV rates in all groups, but there were no significant differences between dosing ranges.[361] Both studies suggest palonosetron may be an effective antiemetic in children with minimal adverse effects, but a minimum effective dose has yet to be established (evidence A2).

Dexamethasone and Combination Therapy. Dexamethasone (0.15 mg/kg) is a safe and efficacious antiemetic that has been well studied in children. A meta-analysis of 13 RCT's and 2000 patients found significantly reduced rates of PONV in children receiving single pharmacologic prophylaxis with dexamethasone. This same study also found a greater reduction when combined with ondansetron (evidence A1, Table 5).[196] There is now conflicting evidence with regards to combination therapy of dexamethasone when combined with droperidol. A double-blinded RCT evaluating 300 children scheduled for tonsillectomy found the combination of dexamethasone (0.25 mg/kg) and ondansetron (0.15 mg/kg) to be more effective than the combination of dexamethasone (0.25 mg/kg) and droperidol (10 µg/kg).[365] A second study evaluated triple combination therapy of dexamethasone (0.125 mg/kg), ondansetron (0.1 mg/kg), and droperidol (50 µg/kg) and found no difference in efficacy when compared to the combination of dexamethasone and ondansetron alone.[366] Both studies suggest that droperidol may be of limited efficacy in children.

Nonpharmacological Therapies in Children. In a recent study, Moeen[367] studied the adequacy of acupuncture for tonsillectomy in a prospective randomized double-blind study involving 120 ASA physical status I–III children aged 2–8 years. One group received 0.15 mg/kg of dexamethasone immediately after induction along with sham acupuncture at point PC6 bilaterally and also CV13. The other group received saline placebo and real acupuncture bilaterally. There was no difference in vomiting at 0–6, 6–24, and 24 hours postoperatively (evidence A3).

Guideline 5. Provide Antiemetic Treatment to Patients With PONV Who Did Not Receive Prophylaxis or When Prophylaxis Failed

When PONV prophylaxis has failed, patients should receive antiemetic treatment from a different pharmacological class to the PONV prophylaxis. Administering repeated dose of antiemetics from the same class within 6 hours does not confer additional therapeutic benefit when compared to placebo (evidence A2).[368,369] If more than 6 hours has elapsed, administration of a second dose of 5-HT$_3$ receptor antagonist or butyrophenone may be considered if no other alternatives are available.[368]

In patients who did not receive PONV prophylaxis, 5-HT$_3$ receptor antagonists such as ondansetron and ramosetron remain the first-line pharmacotherapy for treating established PONV. Recommended treatment rescue antiemetic regimens include ondansetron at 4 mg dose administered orally or IV,[218] ramosetron at 0.3 mg IV,[218] granisetron 0.1 mg and tropisetron 0.5 mg,[370] as well as promethazine 6.25 mg IV.[277,278] In an RCT comparing ondansetron 4 mg to haloperidol 1 mg, the authors reported largely comparable treatment response. However, the haloperidol cohort demonstrated significantly more sedation.[202]

There is also emerging evidence for the use of NK1 receptor antagonist in treating established PONV. Vestipitant, at the doses of 4–36 mg, has demonstrated noninferiority when compared to ondansetron in patients who failed PONV prophylaxis.[228]

Other options for treating established PONV include amisulpride 5–10 mg[188] and droperidol 0.625 mg IV.[371] The use of propofol 20 mg as a rescue antiemetic in the PACU setting has been reported in the past; however, the therapeutic effect is likely to be brief and should be used with caution.[372,373]

Several studies have shown that combination therapy with multiple antiemetics may be more effective in treating established PONV. For example, ondansetron + droperidol + dexamethasone is more effective than ondansetron + droperidol[332]; and palonosetron + dexamethasone is more effective than palonosetron alone.[161] In addition, midazolam 30 µg/kg plus ondansetron was superior to ondansetron alone.[291] There is currently limited evidence as to what is the optimal combination therapy for established PONV, therefore clinician discretion is advised, and the antiemetics used in combination therapy should be selected from different classes.

A Cochrane review on the use of aromatherapy for the treatment of PONV reported that isopropyl alcohol therapy appears to reduce the duration as well as the severity of nausea compared to placebo and conventional pharmacotherapy.[302] Another SRMA investigated the use of ginger for the treatment of PONV, and reported a small reduction of nausea score with ginger compared to placebo.[303] Coloma et al[374] conducted a clinical trial which compared the use of PC6 acupressure, ondansetron, or both for the treatment of established PONV after laparoscopic surgeries, and found that PC6 acupressure was comparable to ondansetron for the treatment of established PONV, and combination of PC6 acupressure and ondansetron was associated with significantly higher response rate.

In addition to providing rescue antiemetics in patients experiencing PONV, patient should be evaluated for reversible causes of PONV, such as excessive opioids, mechanical bowel obstruction, or blood in the pharynx.[3]

Postdischarge Nausea and Vomiting. It is estimated that in ambulatory surgeries, approximately 17% of patients experience nausea and 8% of patients experience vomiting after discharge. Despite earlier data suggesting that TIVA may be associated with lower incidence of PDNV,[375] a recent SRMA concluded that TIVA and volatile anesthesia were associated with comparable risk of PDNV.[376]

There has been limited new evidence on the prevention of PDNV since the last consensus guideline. The current evidence supports the use of multimodal antiemetics for the prevention of PDNV. An RCT compared the use of IV ondansetron alone to IV dexamethasone, IV ondansetron and ondansetron tablet after discharge, and reported significantly lower rate of PDNV in the latter.[377] Other trials have compared ondansetron monotherapy to combination therapy of ondansetron plus NK1 receptor antagonist (aprepitant and casopitant) and reported that combination therapy was associated with significantly lower rate of PDNV,[120,170] while haloperidol plus dexamethasone was associated with lower rate of PDNV than either agent alone.[378]

Guideline 6. Ensure General Multimodal PONV Prevention and Timely Rescue Treatment Is Implemented in the Clinical Setting

This section was introduced at the second iteration of this consensus to emphasize the importance of implementing PONV prevention and treatment strategies in the clinical setting. While risk-adapted protocols are more cost-effective and will likely lead to better patient outcomes when implemented successfully (B2),[60] the compliance with such protocols may not be optimal in a busy clinical environment. Indeed, there is still evidence that implementation is the weakest part in the process from generating evidence to improving health care. Recent publications concluded that “Adherence to PONV prophylaxis guidelines … is still remarkably low,”[379] with less than half of medium to high-risk patients receiving the appropriate prophylaxis.[380] Similar findings were reported in the pediatric population.[381] Since the 2014 consensus guideline, our expert consensus recommendation has been that general multimodal PONV prophylaxis should consist of at least 2 PONV prevention interventions for all patients.[3,13]

Adoption of a multimodal prevention strategy as the de facto practice has several advantages. It minimizes the risk that moderate- to high-risk patients receive suboptimal prophylaxis, and it also minimizes the risk of low-risk patients receiving single treatment that is not effective for the individual.[13,382] In addition, general adoption of a multimodal prevention strategies may facilitate clinical implementation of PONV guidelines,[383] and have been used successfully in a number of other ERPs.[384,385]

In this iteration of the guideline, we have reduced the threshold for administering multimodal PONV prophylaxis to patients with any risk factors, based on expert consensus, with the aim of making multimodal PONV prophylaxis an integral part of anesthesia[382] (Figure 6). In accordance with the recommendations made in this update (guidelines 3 and 4), we would also suggest, based on expert consensus, that high-risk male patients should receive 3 or more antiemetic prophylaxis (eg, “always sick after anesthesia” or presenting with 3 or 4 risk factors).

Clinical PONV Protocols and Algorithms to Implement PONV Policies. We recommend that PONV management protocols or algorithms should make it clear that the individual’s risk of PONV should be assessed to identify the high-risk patients who may require additional prophylaxis.[2] In addition to the patient’s level of PONV risk, the PONV management strategy should take into account patient’s choice, cost-effectiveness of the treatment at the institution, and patient’s preexisting conditions (such as the risk of prolonged QT, Parkinson, and closed-angle glaucoma).[2] This would minimize the risks associated with antiemetic administration, while ensuring that high-risk patients are managed appropriately; and is likely to be the most cost-effective strategy.

Clinical Effectiveness of PONV Protocols. While the intrinsic efficacy of an intervention is fairly consistent, effectiveness is influenced by institutional compliance,[386] disparity between the 2 contributes to the gap between advances in PONV research and the persistent incidence of PONV in clinical practice. Despite the efforts to make PONV management guidelines readily available, its clinical implementation remains poor in both adults and pediatric populations.[387,388] With the expanding role of the electronic medical record systems, some have suggested using of electronic reminders to improve the adherence to PONV guidelines.[389,390]

Timely treatment of PONV requires vigilance by the health care providers. However, it has been shown that PONV symptoms are frequently missed, particularly nausea. One observational study has reported that only 42% of PONV episodes were recognized in the PACU, with 29% recognized in surgical units.[391]

It has been shown that even with intensive training and education, the tendency to continue with de facto standard practice continues, and the adherence to risk-adapted PONV management protocol remains poor (between 35% and 50% compliance).[392,393] This makes it unlikely that lack of education is the cause for deviation from guidelines. Identifying and addressing the resistance to change seems to be the key in implementing guidelines effectively.

The Acquisition Costs of Antiemetics. The cost of antiemetic medications is a key factor to consider when designing a PONV management guideline, and the cost can vary significantly depending on the country, as well as the price negotiation of the individual institution. Since the last iteration of our consensus guideline, generic versions of palonosetron have become commercially available in the United States; this will likely have significant impact on its cost-effectiveness as well as the clinical utilization.

Potential for Adverse Effects. The adverse effects of antiemetics have been studied and reported in numerous clinical trials.[102] Using the lowest recommended dose of antiemetics whenever possible and taking into account the patients' medical history and drug class-specific adverse effects should limit the incidence of adverse effects.

Clinical Applicability and Compliance With Guideline. To minimize the incidence of PONV at an organizational level, introduction of PONV management guideline needs to be followed by regular compliance and outcome measurements. This will allow for improvement of the guideline as well as its adherence in the clinical setting.

To further add to the acceptance of combination therapy for the prevention of PONV, the Centers for Medicare & Medicaid Services (CMS) in the United States has established a quality measure for the purpose of reducing the incidence of PONV through a merit-based incentive payment system (MIPS). MIPS 430 identifies the percentage of adult patients who undergo a surgical procedure with 3 or more risk factors for PONV and have received combination therapy of at least 2 antiemetic agents of different classes. CMS cites the 2014 Consensus Guideline as the clinical recommendation statement used in establishing the measure.[394]

Guideline 7. Administer Multimodal Prophylactic Antiemetics in Enhanced Recovery Pathways

Place of the PONV Management in the General Framework of ERPs. Enhanced recovery is an evolving perioperative care concept.[395,396] In 2016, the American Society for Enhanced Recovery (ASER) released an Expert Opinion Statement concluding that "all patients should receive PONV prophylaxis during the perioperative period. The number of medications used for treatment and prophylaxis should be determined by the number of modifiable and nonmodifiable risk factors; medications used should represent different mechanisms of action in an attempt to achieve multimodal benefit."[397] The panel agrees with the statements.

PONV Management in ERPs Specific to the Type of Surgery. ERPs for various types of surgery include specific recommendations for PONV management.[397,398] Interventions which reduce the baseline emetogenic risk factors, such as the use of propofol TIVA, minimal preoperative fasting, carbohydrate loading, adequate hydration, and the use multimodal opioid-sparing analgesia are recommended.[399] Similar to our general recommendation, we recommend that all ERP patients should receive at least 2 agents for PONV prophylaxis, with additional antiemetics in patients who are high risk. Treatment of established PONV should be prompt and aggressive.[400] For each surgery type, the emetogenicity of the procedure, availability of effective RA technique, and expected course of postoperative recovery should be considered to optimize the management of PONV.

The introduction of a colorectal ERP with general multimodal PONV prophylaxis significantly reduced the rate of PONV[401] and may reduce the risk of readmission.[402] Several enhanced recovery consensus guidelines recommend the implementation of general multimodal prophylaxis with baseline risk reduction interventions for the prevention of PONV in patients undergoing gastrointestinal surgery.[403,404] The ERPs for colorectal surgery patients are applicable to pancreatic surgery.[405,406]

In breast surgery for cancer, a literature review[407] confirms that the use of a paravertebral block (PVB) before the surgery reduces the incidence of PONV.[408] The same is true for the pectoral nerves block (PECs).[409] Other effective interventions include non-opioid analgesia and multimodal PONV prophylaxis.[258,410,411]

In orthopedic surgery, there are limited prospective data on PONV management in the context of ERPs,[412] as pain and weakness are the main reason for delayed postoperative discharge.[413] In a prospective before-and-after study (103 vs 105 patients), introduction of perioperative interventions, including multimodal analgesia, opioid-sparing analgesia, and general antiemetic prophylaxis significantly decreased PONV on POD 1 (relative risk = 0.57, 95% confidence interval [CI], 0.43–0.76).[414]

For gynecologic/oncologic surgery, general multimodal PONV prophylaxis is again recommended; regional interventions (eg, TAP blocks) may decrease opioid use and postoperative pain, but this may not directly translate into a PONV advantage in all cases.[415,416]

For CD, specific risk factors include neuraxial anesthesia, hypotension, reduced cardiac output from aortocaval compression, surgical stimulation, use of uterotonics, and post-CD analgesia with neuraxial opioids. A multimodal approach to PONV prevention is the standard of care.[417]

In radical cystectomy for bladder cancer, the ERAS Society recommendations related to PONV include the use of minimally invasive surgery, early oral intake, liberal use of antiemetics, chewing gum, prokinetic agents, and opioid-sparing analgesia to minimize PONV and postoperative ileus.[418] Besides antiemetics, Doppler-guided fluid management reduces PONV[419] as does the stenting of the ureteroileal anastomosis.[420–422]

A recent prospective observational study on ERPs after cardiac surgery reported that regular IV ondansetron prophylaxis for the first 48 hours did not reduce POV and only lower incidence of nausea on POD 3, suggesting the need for a multimodal approach.[423]

In laryngeal surgery patients, PONV prophylaxis with IV ondansetron (4 mg) and dexamethasone (4 mg) 2 hours before the end of surgery is effective.[424]

In multilevel spinal surgery, implementation of a multimodal analgesia and multimodal PONV management protocol significantly reduce postoperative complications, including PONV.[231]

In summary, the PONV management strategies implemented in the published ERPs are largely similar to the principle of risk reduction, prophylaxis, and treatment discussed in our consensus guideline. It is therefore the panel's consensus that the content of our guidelines could be applied to ERPs.

Research Agenda for PONV

Since the publication of the previous consensus guideline, there have been significant research projects for the management of PONV, particularly around the newer antiemetics such as amisulpride, palonosetron, and NK1 receptor antagonists, as well as research evaluating the role of PONV management as part of ERPs.

On the other hand, adherence to PONV prophylaxis protocols remains a significant challenge. As recommended by our previous guideline and work of others, the use of multimodal antiemetic strategy as general prophylaxis is increasingly common.[3,382]

However, there are very few studies directly comparing the efficacy of a risk-based "restrictive" antiemetic prophylaxis approach to a more liberal multimodal antiemetic prophylaxis approach.

Since the last iteration of the guideline, a number of new antiemetic combinations has been proposed. However, the optimal multimodal prophylaxis regimen as well as the optimal number of antiemetics in combination therapies remains unclear due to lack of head-to-head comparisons.[159,170,171,288] Weibel et al[102] are conducting a network meta-analysis on the efficacy of monotherapies as well as combination therapies, their findings will likely shed some light on the efficacy comparisons between some of the combination therapies. There is also insufficient evidence to determine the choice of optimal combination therapy for the treatment of established PONV. Head-to-head comparisons between common combination therapies would be invaluable.

Another aspect that requires additional study is the role of nonpharmacological interventions such as PC6 acupoint stimulation. While PC6 stimulation has been shown to reduce the risk of PONV, its added value as part of multimodal treatment is unclear. In addition, there are numerous modalities of stimulation, such as needle acupuncture, acupressure, needle, or transcutaneous electrical stimulation.[294] Further research is needed to distinguish between the efficacies of the different stimulation modalities.

Similarly, while perioperative supplemental fluids have been shown to reduce the risk of PONV, there is conflicting evidence on the choice between colloids and crystalloids.[74] In addition, the optimal volume and time of administration are unclear. Additionally, liberal fluid administration can also be associated with postoperative complications.[425] More studies are needed to assess the risk-benefit profile of fluid therapy and PONV.

There is also emerging evidence that antiemetic efficacy may be influenced by gene polymorphisms as well as variation in gene expression (epigenetics).[426] For example, cytochrome P450 2D6 is involved in the metabolism of several 5-HT_3 receptor antagonists, and ultrarapid metabolizer phenotype may be associated with reduced antiemetic efficacy of ondansetron, tropisetron, and others.[427] Another example is the polymorphisms of the serotonin-transporter-linked polymorphic region, which have been associated with increased risk of PONV.[428] Dopamine receptor 2 gene polymorphism has also been linked to increased risk of PONV.[429] More studies are needed in this area. In addition, there are studies which suggest an association between patient ethnicity and the risk of PONV,[430] and additional studies are needed to confirm this association.

Finally, both the American Society of Anesthesiologists Task Force on Acute Pain Management and our group have advocated for using $P < .01$ as the significance level for statistical analysis to minimize the risk of false-positive findings.[25] However, most recent studies have used a significance level of $P < .05$. We would strongly encourage prospective investigators to use a significance level of $P < .01$, with confidence intervals, in future studies; so the clinical relevance of the study findings could be contextualized.

CONCLUSIONS

The updated PONV consensus guidelines are designed to provide comprehensive evidence-based clinical recommendations on the management of PONV in adults and children. Prevention of PONV should be considered an integral aspect of anesthesia, achieved through risk assessment, baseline risk prevention, as well as pharmacoprophylaxis. One major change in this iteration of the guideline is that in adults, the panel consensus is now to implement multimodal PONV prophylaxis in patients with 1 or 2 risk factors, in an attempt to reduce risk of inadequate prophylaxis. However, clinician discretion is advised in assessing the benefits and risks of multimodal prophylaxis based on patient and surgical factors. Combination therapy should consist of drugs from different classes, using minimum effective doses, and the choice of drugs will be determined by patient factors as well as institutional policy and drug availability. In children, we still recommend the use of multimodal PONV prophylaxis in those at moderate or high risk and recommend the use of a 5-HT_3 receptor antagonist plus dexamethasone, with opioid and volatile anesthesia sparing strategies as first-line interventions.

In patients who develop PONV, prior prophylaxis administration should be assessed, and rescue treatment should consist of drugs from a different class than those used for prophylaxis. If more than 6 hours have elapsed since the administration of a short-acting antiemetic (such as ondansetron or droperidol), a repeat dose could be considered if no other options are available. Unlike PONV prophylaxis, the evidence for the efficacy of PONV rescue treatments is limited, both in terms of monotherapy and combination therapy. However, more data are available for treatment of established PONV (eg, amisulpride). Clinicians are advised to use their judgment, considering the patient factors, administration of prophylaxis, and institutional drug availability.

PONV management is a vital component of ERPs. With multimodal PONV prophylaxis now recommended for all adult surgical patients with any risk factors, the panel recommends that the principles of PONV management as discussed in this consensus guideline should also apply to the management of PONV within ERPs.

At an institutional level, design and implementation of a PONV management protocol will need to take into account the cost-effectiveness of treatments and availability of drugs. As individual patients may not respond to certain classes of antiemetics, we recommend that institutions should provide antiemetics from at least 4 classes. In a busy clinical environment, implementation of a more liberal multimodal prophylaxis with at least 2 drugs, and an additional antiemetic in high-risk patients, as well as continued compliance monitoring may be a more judicious approach in optimizing PONV care.

APPENDIX 1: PROFESSIONAL SOCIETY ENDORSEMENTS

This set of guidelines have been officially endorsed by the following professional organizations:

- American Society for Enhanced Recovery
- American Society of Health Systems Pharmacists
- American Society of Peri Anesthesia Nurses
- American Society of Anesthesiologists
- American Academy of Anesthesiologist Assistants
- American Association of Nurse Anesthetists
- American College of Clinical Pharmacy
- American College of Clinical Pharmacy Perioperative Care Practice and Research Network
- Australian Society of Anesthetists
- Brazilian Society of Anesthesiology
- Chinese Society of Anesthesiology
- European Society of Anesthesiology
- Indian Society of Anesthesiologists
- Japanese Society of Anesthesiologists
- Korean Society of Anesthesiologists
- Malaysian Society of Anesthesiologists
- Royal College of Anesthesiologist Thailand
- Singapore Society of Anesthesiologists
- Society for Ambulatory Anesthesia
- Society of American Gastrointestinal and Endoscopic Surgeons
- Society for Pediatric Anesthesia
- South African Society of Anesthesiologists
- Taiwan Society of Anesthesiologists

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