A Practical 5-Step Approach to Nausea and Vomiting

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Abstract

Nausea and vomiting (N/V) are common presenting complaints in the outpatient and inpatient settings. These symptoms can be associated with high morbidity and poor quality of life, particularly in those with chronic symptoms. The clinical approach to N/V can be challenging, given the numerous possible underlying causes as well as the vast array of diagnostic and therapeutic options. In this concise review, we provide a practical 5-step approach to the clinical evaluation and treatment of N/V, suitable for application in the primary care and subspecialty settings. The 5-step approach includes (1) defining what the patient means by N/V, (2) determining whether symptoms are acute or chronic, (3) considering medication or toxin adverse effects, (4) using the patient’s presentation, severity of symptoms, and physical examination findings to formulate a differential diagnosis and to guide evaluation, and (5) directing treatment on the basis of knowledge of neurotransmitters and receptors involved in the emetic pathways. We discuss the pathophysiology (neuronal pathways and neurotransmitters), differential diagnosis (medication and toxin adverse effects, neurologic causes, gastrointestinal diseases, metabolic and endocrine conditions, and psychogenic disorders), initial evaluation and risk...
NAUSEA AND VOMITING

Nausea and vomiting (N/V) are commonly encountered complaints in medicine. These symptoms are often associated with high morbidity and poor quality of life and carry significant economic burden.\(^1\)\(^-\)\(^3\) Whereas N/V are common presenting symptoms, their evaluation and management can be daunting even for the most astute clinician. This is in part due to the breadth of possible underlying causes and myriad diagnostic tests that could be pursued for work-up of symptoms. In this review, we provide a practical 5-step approach to N/V (Figure 1).

DEFINITIONS

Step 1 is to define what the patient means by N/V. Distinguishing N/V from other conditions, such as retching, regurgitation, and rumination, is critical. Nausea is a subjective sensation of an uneasy feeling in the throat or epigastrium that often immediately precedes vomiting. Vomiting is a highly specific physical event resulting in the rapid and forceful oral expulsion of gastric contents accompanied by contraction of abdominal musculature.\(^4\) Retching is active and repetitive spasmodic contraction of abdominal musculature with the glottis closed but without expulsion of gastric contents. In contrast, regurgitation is the passive retrograde movement of esophageal or gastric contents back into the mouth without diaphragmatic or muscular activity characteristic of vomiting. Regurgitation is a cardinal symptom of gastroesophageal reflux disease. Rumination is the regurgitation of partially digested food back into the mouth through a voluntary increase in abdominal pressure. In patients with rumination, abdominal pain or pressure is often relieved by regurgitation. The symptoms of regurgitation and rumination may be misinterpreted by patients as N/V; therefore, the first step is distinguishing vomiting from regurgitation and rumination as the evaluation and treatment of these conditions are markedly different.

PATHOPHYSIOLOGY

The pathophysiologic mechanism of N/V is complex. However, a basic understanding of the neuroanatomic pathways involved allows informed treatment decisions. A variety of signals and neurotransmitters converge on the “vomiting center” in the dorsal lateral reticular formation of the medulla (Figure 2). The complex neurochemistry of this emetic reflex necessitates different pharmacologic approaches to control vomiting from various causes. The cerebral cortex, gastrointestinal tract, vestibular system, and chemoreceptor trigger zone (CTZ) are major sources of afferent pathways to the vomiting center. These signals synapse on the solitary nucleus of vagus, subsequently stimulating the emetic center.\(^5\) Efferent pathways from the emetic center then coordinate the contraction of abdominal and chest wall musculature that gives rise to vomiting. The highly coordinated series of events of the emetic sequence include cessation of antral contractions, relaxation of stomach, increase in pyloric tone, lower esophageal sphincter relaxation, and contraction of the abdominal wall and diaphragm, all of which contribute to the expulsion of gastric contents into the oropharynx. Many neurotransmitters are involved in coordinating the emetic sequence, including serotonin, acetylcholine, dopamine, histamine, substance P, cortisol, and endocannabinoids (Figure 2).\(^6\) Knowledge of neurotransmitters and receptors in the central and
peripheral pathways of N/V enhances appropriate use of pharmacotherapeutics.

DIFFERENTIAL DIAGNOSIS
The differential diagnosis of N/V is extensive. Step 2 is to assess symptom duration and to determine whether the N/V is acute or chronic. Acute N/V is defined by symptom duration of 7 or fewer days, in contrast to chronic N/V, defined by symptom duration of 4 weeks or more.7 Most cases of acute N/V represent a short-lived medical condition (eg, viral gastroenteritis), a self-limited somatic disorder (eg, musculoskeletal trauma; acute myocardial infarction), or a transient medication adverse effect. Therefore, acute N/V may often be treated symptomatically without pursuing an in-depth causal evaluation. For chronic N/V, it is often useful to consider the following major etiologic categories: medication adverse effects, neurologic causes, gastrointestinal diseases, metabolic and endocrine conditions, and psychogenic disorders (Figure 3).

Medications and Toxins
Step 3 is to consider medication or toxin side effects. Reactions to medication are a common cause of N/V, especially within days after initiation of therapy, although the onset of symptoms may be insidious. Many different medications may cause N/V; common culprits include nonsteroidal anti-inflammatory drugs, antiarrhythmic agents, antibiotics, antiepileptic drugs, opiates, and levodopa. Excessive and long-term cannabis use may lead to cannabinoid hyperemesis syndrome (CHS; see later).

Medications and toxins probably lead to N/V by stimulating the CTZ located in the area postrema at the ventral aspect of the fourth ventricle.5 In addition, both chemotherapy and radiation therapy are well-known causes of N/V. Risk factors for chemotherapy-induced nausea and vomiting (CINV) include female sex, younger age, co-morbid anxiety, and prior history of N/V.8 Postoperative N/V is another important consideration. Symptoms typically begin within 24 hours following a surgical procedure.
procedure and may be triggered by anesthetics, opioids, and other adverse drug reactions.

**Neurologic**

Various neurologic disorders can cause N/V. Any condition increasing intracranial pressure, such as central nervous system mass lesions, infection, hydrocephalus, idiopathic intracranial hypertension, and hemorrhage, may produce emesis with or without nausea. Labyrinthine causes of N/V include Ménière disease, vestibular schwannoma, and benign paroxysmal positional vertigo. The N/V of motion sickness is caused by repetitive movements activating vestibular nuclei. In addition, migraine headaches and seizures are frequently associated with N/V. Both acute and chronic pain may be associated with N/V.

**Gastrointestinal**

Gastrointestinal irritants cause release of serotonin (5-HT₃) from enteroendocrine cells of the intestinal epithelium, which stimulates 5-HT₃ receptors on afferent vagal fibers. This activation is the major factor initiating the vomiting reflex after ingestion of noxious substances or related to gastrointestinal mucosal ulceration, inflammation, and luminal distention. The different gastrointestinal diseases causing N/V can be separated into acute and chronic conditions. Acute symptoms may result from infections (eg, gastroenteritis), inflammatory diseases (eg, pancreatitis or appendicitis), and intestinal obstruction (eg, volvulus, intussusception, or strangulated hernia). Chronic N/V may be caused by dyspepsia, gastroparesis, and chronic intestinal pseudo-obstruction, among others.
Metabolic and Endocrine

Metabolic and endocrine derangements cause afferent input into the vomiting center by stimulating the CTZ in the area postrema. Many metabolic and endocrine conditions may cause N/V, including diabetic ketoacidosis, uremia, adrenal insufficiency, hyperparathyroidism, and thyroid disorders. Pregnancy is the most common endocrine cause of N/V, occurring in up to 50% to 75% of women, whereas hyperemesis gravidarum occurs in only 1% to 5% of pregnancies and is treated with pyridoxine (vitamin B6). Electrolyte abnormalities, such as hyponatremia, hypokalemia, and hypercalcemia, may also be manifested with N/V. Less common causes include paraneoplastic syndromes and hematologic disorders, including acute intermittent porphyria.

Psychogenic

A multitude of psychiatric conditions can be associated with N/V because of emotional or physical stressors. These disorders may include anxiety, depression, anorexia nervosa, and bulimia nervosa.

SELECTED NAUSEA AND VOMITING SYNDROMES

Functional vomiting describes frequent episodes of recurrent vomiting in the absence of organic, psychiatric, systemic, or other metabolic diseases that could otherwise explain the symptoms. Cyclic vomiting syndrome is manifested with stereotypical and recurrent discrete episodes of vomiting with variable symptom-free periods. The episodes of vomiting are usually similar in onset, symptoms, and duration. Cannabinoid hyperemesis syndrome is characterized by episodes of vomiting occurring from prolonged cannabis exposure with symptoms that resolve after cannabis cessation. Opioid-induced N/V can occur shortly after the offending medication is taken and is thought to be mediated by reduced
gastrointestinal motility, activation of the CTZ, and vestibular system. Conditioned N/V, also known as anticipatory or learned N/V, refers to symptoms that are triggered by specific environmental sensory stimuli.

INITIAL EVALUATION

The initial evaluation of N/V consists of a comprehensive history and physical examination. Step 4 is to use the patient’s presentation, severity of symptoms, and physical examination findings to formulate a differential diagnosis and to guide further evaluation with laboratory, imaging, and procedural tests.

Patient’s History

The history is the diagnostic framework for the evaluation of N/V. It is important to clarify details about the onset of symptoms (abrupt vs gradual), timing (in relation to food, frequency), nature of emesis (undigested or partially digested food, presence of bile, volume), and associated symptoms (abdominal pain, weight loss, early satiety, bloating, change in bowel habits, and neurologic deficits). The description of vomitus, timing of vomiting, and associated symptoms are often helpful in suggesting a cause (Table 1). An extensive review of the patient’s comorbid diseases, medication list, and substance use history (e.g., alcohol, tobacco, marijuana) should be performed.

Physical Examination

The physical examination should focus on signs of dehydration (skin turgor and mucous membranes) and assessment of orthostatic vital signs, especially in the inpatient setting. The presence of lymphadenopathy, jaundice, abdominal masses, and signs of depression and anxiety should be noted. Systemic features, such as increased skin and mucosal hyperpigmentation in Addison disease, tremor or lid lag in thyrotoxicosis, and lanugo with calluses on the dorsum of the hands in self-induced vomiting, can provide important diagnostic clues.

The abdominal examination is particularly important and can further help narrow the diagnosis with findings such as a succussion splash, suggesting gastric outlet obstruction. In those presenting with neurologic and vestibular symptoms, a cranial nerve and neurologic examination may be indicated. Vestibular dysfunction has been reported in up to 26% of patients with chronic N/V who initially presented to a gastroenterologist.

Laboratory Tests

Initial laboratory evaluation includes complete blood count and electrolyte analysis. Additional laboratory tests should be guided principally by history and physical examination. Examples include a pregnancy test for women of childbearing age, inflammatory markers (C-reactive protein) for a suspected

<table>
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<tr>
<th>Features</th>
<th>Possible cause</th>
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| Description of vomitus | • Partially digested food several hours after meal: consider gastroparesis or gastric outlet obstruction  
  • Bilious emesis: consider small bowel obstruction or intestinal pseudo-obstruction |
| Timing of vomiting | • Morning emesis before breakfast: consider pregnancy, uremia, alcohol ingestion, increased intracranial pressure  
  • Episodes of severe unrelenting vomiting: consider cyclic vomiting syndrome and cannabinoid hyperemesis syndrome |
| Associated symptoms | • Headache, vertigo, focal neurologic signs: consider central nervous system process or vestibular process  
  • Intermittent abdominal pain that improves after vomiting: consider small bowel obstruction  
  • Weight loss: consider malignant disease |

### TABLE 1. Features That May Suggest a Specific Cause of Nausea and Vomiting
inflammatory process, serum drug levels or urine drug screen for concern of ingestion, pancreatic or hepatic enzyme activities for gastrointestinal processes, and glycosylated hemoglobin level in patients with diabetes. Other laboratory tests that may be considered include thyroid-stimulating hormone level (hypothyroidism), morning cortisol level (adrenal insufficiency), and serum calcium concentration (hypercalcemia).

**Imaging and Further Tests**
The initial diagnostic evaluation should be directed by history, physical examination, and laboratory tests. For patients with mild N/V without alarm symptoms, the initiation of antiemetic therapy without additional imaging may be considered. For those with a likely gastrointestinal cause, abdominal radiography may be the first diagnostic imaging test of choice. In other cases, cross-sectional imaging of the abdomen with computed tomography may be necessary. For those with concomitant dysphagia, esophagoduodenoscopy or esophageal manometry can be considered once structural or anatomic causes are ruled out. For patients with suspected gastroparesis, a gastric emptying study may be performed. In those with suspected central nervous system causes, brain magnetic resonance imaging may be the next step.

Once a comprehensive history, physical examination, and diagnostic evaluation have been performed and found to be unremarkable, a psychogenic assessment should be considered in those with chronic, unexplained N/V.

**MANAGEMENT AND TREATMENT**
The first step in managing patients includes discontinuation of suspected offending medications when this can be done safely. This is especially important when there is a temporal relationship between medication initiation and symptom onset. Dietary modification can also be considered, with careful attention to adequate oral intake and nutritional support. When a specific diagnosis of N/V is established, management is directed to treatment of the underlying condition.

**Pharmacologic Therapies**
After appropriate replacement of fluid and electrolytes, a variety of antiemetic and prokinetic agents may be considered for the treatment of N/V (Table 2). Although many agents can successfully manage acute N/V, the management of chronic symptoms may be more challenging. Step 5 is to direct treatment on the basis of knowledge of neurotransmitters and receptors involved in the central and peripheral emetic pathways. The 5-HT₃ antagonists act through

<table>
<thead>
<tr>
<th>Medications</th>
<th>Adverse effects</th>
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<tbody>
<tr>
<td>Serotonin 5-hydroxytryptamine antagonists (ondansetron, granisetron)</td>
<td>Mild headache, constipation, QT interval prolongation</td>
</tr>
<tr>
<td>Phenothiazines (prochlorperazine, promethazine)</td>
<td>Extrapyramidal symptoms (dystonia, tardive dyskinesia), QT interval prolongation</td>
</tr>
<tr>
<td>Anticholinergic (scopolamine)</td>
<td>Dry mouth, vision changes, urinary retention, constipation</td>
</tr>
<tr>
<td>Antihistamines (medazine, diphenhydramine, cyproheptadine, hydroxyzine)</td>
<td>Drowsiness, xerostomia</td>
</tr>
<tr>
<td>Corticosteroids (dexamethasone, methylprednisolone)</td>
<td>Hypertension, diabetes, metabolic bone disease, weight gain, insomnia, mood changes</td>
</tr>
<tr>
<td>Benzodiazepines (lorazepam, alprazolam)</td>
<td>Sedation, unsteadiness (older patients), dizziness, dependence</td>
</tr>
<tr>
<td>Neurorokin 1 receptor antagonists (aprepitant, fosaprepitant)</td>
<td>Asthenia, diarrhea, headache</td>
</tr>
<tr>
<td>Benzamides (metoclopramide, trimethobenzamide)</td>
<td>Extrapyramidal symptoms (dystonia, tardive dyskinesia), hyperprolactinemia</td>
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central antagonism in the CTZ and peripheral antagonism on intestinal vagal afferents. They are highly effective in treating N/V because of activation of both central and peripheral pathways by broad 5-HT3 receptor expression.17 QT interval prolongation is an important consideration, particularly in patients with arrhythmias and those concurrently taking additional QT-prolonging drugs.

The phenothiazines (eg, prochlorperazine, promethazine) and butyrophenones (eg, droperidol, haloperidol) block D2 dopaminergic receptors and are useful in patients with vomiting of central origin, as in migraine headaches, motion sickness, and vomiting related to toxic agents.18 The potential of extrapyramidal adverse effects is a concern; risk is dependent on the patient’s age as well as on medication dose and is reported as high as 25%.6,15 An attractive alternative is the second-generation neuroleptic olanzapine because of its effective antinausea and antiemetic action and lower risk of extrapyramidal adverse effects.

Anticholinergic and antihistamine medications (eg, diphenhydramine, meclizine) exert their action through central anticholinergic (M1 receptor) and antihistamine (H1 receptor) effects. They can be particularly effective for treating N/V associated with vertigo and motion sickness by acting on the vestibular system and CTZ.19 However, these agents should be used with caution in the elderly as they can precipitate confusion, urinary retention, vision changes, and constipation. Metoclopramide is a potent antiemetic with prokinetic properties and is effective for gastroparesis. Its mechanism of action involves vagal and central 5-HT3 and D2 receptor antagonism. Long-term use is limited by potential extrapyramidal adverse effects (akathisia, parkinsonism, and tardive dyskinesia) that may be irreversible.6,18 Neurokinin 1 receptor antagonists work by alleviating the emetic effects of substance P and are Food and Drug Administration approved for the treatment of CINV.19 Of note, there are limited studies directly comparing the effectiveness of these various antiemetic agents.

Conditions such as cyclic vomiting syndrome can be especially challenging to treat. Patient education and behavioral counseling play a central role in the multidisciplinary management of functional and psychogenic disorders of N/V.20 Medications such as olanzapine and mirtazapine can be used for functional N/V, with mirtazapine augmenting appetite in select patients and improving sleep. Patients taking mirtazapine should be monitored for weight gain and mood changes (eg, suicidal ideation). Tricyclic antidepressants may be considered for patients with refractory symptoms despite therapeutic trials of other antiemetic agents.21 Studies suggest that low-dose gabapentin may be effective in the treatment of functional dyspepsia and N/V.22 Pain management is also important as abdominal pain is a frequent symptom in those with chronic N/V. Opioids should be avoided as they can worsen gastric motility and nausea.23 The mainstay of treatment in CHS is cessation of cannabinoid use, and symptoms may take months after cannabinoid discontinuation to improve.

Additional Treatments
Surgical treatment is indicated for certain causes of N/V (eg, gastric outlet obstruction). Enteral nutrition with percutaneous endoscopic gastrostomy or jejunostomy may be considered in those with severe, refractory symptoms or conditions not amenable to surgical resection (eg, metastatic malignant disease). When possible, enteral feeding is preferred to parenteral nutrition. There is an increased risk of complications with parenteral nutrition, including bloodstream infections, metabolic derangements, macronutrient or micronutrient excess or deficiency, and hepatic dysfunction.

In addition, a variety of integrative and alternative therapies have been reported for chronic N/V, including acupuncture, hypnotherapy, herbal supplements such as ginger, and pyridoxine, among others.24 Nonetheless, there is often limited evidence for these therapies based on studies with small sample sizes and inconsistent results. Cannabinoids
have been approved for CINV, although their long-term use may also cause CHS.\textsuperscript{25} In general, cannabinoids should not be used routinely to treat N/V.

CONCLUSION
Nausea and vomiting are complex, multifactorial symptoms. Using a rational 5-step approach can help narrow the large differential diagnosis and direct treatment. A comprehensive history and physical examination form the diagnostic framework for the evaluation of N/V and guide diagnostic testing. Treatment is focused on addressing the underlying disease and alleviating symptoms using antiemetic and prokinetic agents. Complementary and alternative therapies may be considered in those with chronic, refractory symptoms.

Abbreviations and Acronyms: CHS, cannabinoid hyperemesis syndrome; CINV, chemotherapy-induced nausea and vomiting; CTZ, chemoreceptor trigger zone; 5-HT\textsubscript{3}, serotonin; N/V, nausea and vomiting

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