The Palliative Care Approach to Nausea & Vomiting

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Symptoms: General Approach

- Can result from disease or its treatment
- Evaluation based on goals of care
- Base treatment on underlying mechanism if possible or to relief of symptom
Nausea and Vomiting

- Nausea
  - Unpleasant sensation of need to vomit
  - Pallor, sweats, tachycardia, diarrhea

- Common sx in patients with serious illness:
  - 40% of patients at EOL
  - 70% of patients with advanced cancer

One of the most uncomfortable symptoms!
The Triggers of Nausea & Vomiting

- 1st line of defense: Our Senses
- 2nd line of defense: Gut Chemo- and Mechanoreceptors
- 3rd line of defense: Receptors in the brain
- 4th line of defense: Memory, Learned Behavior
Mechanisms of Nausea and Vomiting

- Higher cortical structures
- Chemoreceptor trigger zone (4th ventricle)
  D2, NK1, (5HT3)
- Vestibular system
  Achm, H1
- Vomiting Center:
  (Medulla)
  Achm, H1, (5HT3)
- Mechanical stretch, GI irritation
  5HT3 in GI tract, mechanoreceptors,
  vagal, splanchnic and glossopharyngeal nerves

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Ms. A

- Ms. A is a 43 year-old woman with metastatic breast cancer.
- Her disease has progressed rapidly despite aggressive therapy.
- She recently developed right arm weakness and was found to have brain metastases in addition to bone, liver, and lung metastases.
- Ms. A presents to clinic today complaining of 2 weeks of nausea and vomiting.
Ms. A

- Medications:
  pamidronate, phenytoin, oxycodone prn, ibuprofen, omeprazole, and docusate.

- Exam notable for tachycardia, dry mucosa, normal abdominal exam, and old right arm weakness.
  - Rectal exam: no stool
Questions

- What are the potential causes of Ms. A’s nausea and vomiting?
- Is there any other workup you would like to perform?
- How would you approach a treatment plan?
History

- Onset, frequency, and severity of nausea
- Careful medication review
- Underlying medical illnesses
  - If cancer: type, location, recent treatments (chemo/XRT/surgery?)
- Associated sx's
  - Gastritis, reflux, constipation?
History: Look for Patterns

- Early satiety, bloating, relief of nausea w/ small-volume emesis
  → Gastric stasis
- Colicky abdominal pain, large-volume bilious emesis
  → Gastric obstruction
- Nausea with certain smells or the sight of food
  → Activation of chemoreceptor trigger zone
- Motion-induced nausea, vertigo
  → Vestibular
- Early morning nausea, headaches, impaired cognition
  → Increased ICP
- Anxiety or emotionally induced nausea
  → Cortical
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<th>Element of History or Physical Examination</th>
<th>Suggested Etiology of Nausea and Vomiting</th>
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<td><strong>History</strong></td>
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<td>Large, infrequent vomitus that relieves nausea</td>
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<td>Small-volume emesis</td>
<td>Gastric stasis</td>
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<td><strong>Associated symptoms</strong></td>
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<tr>
<td>Vertigo and symptom association with movement</td>
<td>Vestibular dysfunction</td>
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<td>Morning symptoms with morning headache and neurological symptoms</td>
<td>Increased intracranial pressure</td>
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<tr>
<td>Polyuria, polydipsia</td>
<td>Hyperglycemia or hypercalcemia</td>
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<td>Altered mental status</td>
<td>Uremia, hyponatremia, or increased intracranial pressure</td>
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<td>Neck stiffness</td>
<td>Meningeal disease</td>
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<td>Syncopal episodes, early satiety</td>
<td>Autonomic insufficiency</td>
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<td>Decreased frequency of bowel movements, abdominal fullness, hard stools, straining with defeation</td>
<td>Constipation</td>
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<tr>
<td>Obstipation, crampty abdominal pain</td>
<td>Bowel obstruction</td>
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<tr>
<td>Bloating, early satiety</td>
<td>Gastric stasis</td>
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<tr>
<td>Esophageal burning, sour taste in mouth, worse with lying down</td>
<td>Gastroesophageal reflux disease</td>
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<tr>
<td>Right upper-quadrant pain</td>
<td>Gallbladder or liver disease</td>
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<tr>
<td>Epigastric pain radiating to back</td>
<td>Pancreatititis</td>
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<td>Fever, diarrhea</td>
<td>Gastroenteritis</td>
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<td>Worry, emotional responses</td>
<td>Anxiety</td>
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<td><strong>Physical examination</strong></td>
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<tr>
<td>Orthostatic blood pressure and pulse changes or absence of heart rate variation with Valsalva maneuver</td>
<td>Autonomic insufficiency</td>
</tr>
<tr>
<td>Papilledema, neurological signs</td>
<td>Increased intracranial pressure</td>
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<td>Thrush or herpetic lesions</td>
<td>Oropharyngeal, esophageal irritation</td>
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<tr>
<td>Abdominal distention and abnormal bowel sounds</td>
<td>Bowel obstruction, ileus, or constipation</td>
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<td>Succussion splash</td>
<td>Gastric outlet obstruction</td>
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<tr>
<td>Abdominal masses or ascites</td>
<td>Abdominal malignancy</td>
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<tr>
<td>Marked splenomegaly</td>
<td>Direct bowel compression by spleen</td>
</tr>
<tr>
<td>Fecal impaction on rectal examination</td>
<td>Constipation</td>
</tr>
</tbody>
</table>

*See text for comorbidities and therapies that may directly contribute to nausea.*
Evaluation

- Oral inspection
- Abdominal exam
- Rectal exam (r/o impaction)
- Labs: lytes, BUN, Cr, LFTs, Ca$^{++}$, drug levels
- Imaging
  - KUB or CT abd/pelvis
  - CT brain
Ms. A: Differential Diagnosis

- Medications
  - pamidronate, oxycodone, ibuprofen, phenytoin
- Metastases
  - brain, liver, peritoneum
- Constipation
- Metabolic
  - hyponatremia, uremia, hypercalcemia, liver failure
Nausea/Vomiting Treatment: 2 Approaches

1. Mechanism-based
   - Determine likely etiology and target first medication to the cause
     - 80-90% effective in the palliative care population
   - Elegant
   - Assesses all causes systematically

2. Empiric
   - Typically multiple etiologies
   - Start with a 5HT3 antagonist (ondansetron) or dopamine antagonist (eg haloperidol) regardless of underlying etiology

Wood et al. JAMA 2007;298:1196-1207
Davis and Hallerberg J Pain Sym Man 2010;39:756-67
Mechanism-Based Approach to Initial Management of N/V

1. Thorough evaluation to narrow DDx
2. Determine underlying pathway and neuroreceptor
3. Choose antiemetic targeted against neuroreceptor
4. Initiate antiemetic around-the-clock
5. Titrate antiemetic to max recommended dose if nausea persists
6. Add additional antiemetic aimed at different neurotransmitter if nausea persists
7. Evaluate for additional reversible mechanisms & treat
Mechanisms of Nausea and Vomiting

Higher cortical structures

Chemoreceptor trigger zone
(4th ventricle)
D2, (5HT3), NK1

Vestibular system
Achm, H1

Vomiting Center:
(Medulla)
Achm, H1, (5HT3)

Mechanical stretch, GI irritation
5HT3 in GI tract, mechanoreceptors,
vagal, splanchnic and glossopharyngeal nerves

N/V
Chemoreceptor Trigger Zone

- Most common cause of N/V near end of life
- Mediators
  - Dopamine (D2), serotonin (5HT3), NK1
- Etiologies
  - Drugs: opioids, digoxin, antibiotics, NSAIDS
  - Metabolic: hypercalcemia, hyponatremia, uremia, hepatic failure
  - Bacterial toxins
Chemoreceptor Trigger Zone

Treatment

- Relieve underlying etiology
  - D/C meds, lower dose, PPI if can’t stop NSAID
  - Correct electrolytes

- Treatment:
  - Ondansetron (5HT3)
  - Haloperidol (potent D2 antagonist at CTZ)
  - Prochlorperazine (D2, H1, Achm, 5HT3)
  - Olanzapine (multiple Ds and 5HTs, Achm)
Ms. A: Differential Diagnosis

- Medications
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N/V
Mechanical Stretch, GI Irritation

- **Mediators**
  - 5HT3 in GI tract, GI mechanoreceptors, Vagus nerve (AchM, histamine)

- **Etiologies**
  - Mucosal irritation (e.g. candidiasis, XRT)
  - External irritation (e.g. peritoneal carcinomatosis)
  - GI stretch (e.g. constipation, obstruction)
  - Viscus enlargement (e.g. liver, kidney)
  - Dysmotility (gastric, bowel infiltration, opioids, anticholinergics)
Mechanical Stretch, GI Irritation: Treatment

- Relieve underlying cause
  - Treat constipation, gastroparesis
  - Antibiotics for candidiasis
  - PPI for gastritis
- Ondansetron (5HT3)
  - Note: avoid if patient constipated
- Promethazine (Anticholinergic/antimuscarinic)
- Metoclopramide (for gastroparesis, partial bowel obstruction)
- Olanzapine (multiple Ds and 5HTs, Achm)
Mechanisms of Nausea and Vomiting

Higher cortical structures

Chemoreceptor trigger zone (4th ventricle)
D2, 5HT3, NK1

Vestibular system
Achm, H1

Vomiting Center: (Medulla)
Achm, H1, 5HT2

Mechanical stretch, GI irritation
5HT3 in GI tract, mechanoreceptors, vagal, splanchnic and glossopharyngeal nerves

N/V
Higher cortical structures

- Direct stimulation of vomiting center
- Etiologies:
  - Tumor, mets, bleed, edema, infection
  - Mind: emotions, memory
- Treatment:
  - Dexamethasone 4-16 mg po/iv per day, divide 1-2 times/day
  - Benzodiazepines for anticipatory nausea, anxiety-induced nausea, and refractory nausea
    - Note: No evidence for BZD as sole agent for tx of nausea.
  - Dietary changes for taste and smell
Mechanisms of Nausea and Vomiting

Higher cortical structures

Chemoreceptor trigger zone
(4th ventricle)
D2, 5HT3, NK1

Vestibular system
Achm, H1

Vomiting Center:
(Medulla)
Achm, H1, 5HT2

Mechanical stretch, GI irritation
5HT3 in GI tract, mechanoreceptors, vagal, splanchnic and glossopharyngeal nerves

N/V
Vestibular System

- Mediators: Histamine and Acetylcholine
- Associated with movement
- Etiology:
  - Tumor, mets at base of skull
  - Middle ear disease
  - Stroke
- Treatment:
  - Diphenhydramine
  - Scopolamine patch 1.5mg q3d
  - Promethazine
  - Meclizine
Mechanism-Based Approach to Initial Management of N/V

1. Thorough evaluation to narrow DDx
2. Determine underlying pathway and neuroreceptor
3. Choose antiemetic targeted against neuroreceptor
4. Initiate antiemetic around-the-clock
5. Titrate antiemetic to max recommended dose if nausea persists
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7. Evaluate for additional reversible mechanisms & treat
Intractable Nausea and Vomiting

- Combine antiemetics with different mechanisms of action
- Start with ATC dosing
- Add steroids (dexamethasone)
  - Unclear mechanism of action
  - Less impressive as single agents but quite effective in combination with other agents, such as Ondansetron
  - Good for acute and delayed emesis
Intractable Nausea and Vomiting

- Nontraditional antiemetics:
  - Mirtazapine
    - 5HT3 antagonist. 15-45mg po at bedtime.
    - Can help w/ n/v, insomnia, appetite, mood
  - Olanzapine
    - D2, 5HT3, AchM
    - Can help w/ n/v, delirium, anxiety, insomnia, and cachexia

- Consider bowel obstruction
Nausea and Vomiting

Other Considerations

- Medications
  - Route of administration
  - Frequency of dosing, ATC vs PRN
  - Anticipate nausea triggers and premedicate w/ antiemetic.
  - Cost

- Food
  - Small, frequent, attractive meals
  - Consider odor, fat content
  - Cool carbonated beverages
  - Take medications, except antiemetics, after meals

- Acupuncture, Acupressure

- Imagery

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Nausea and Vomiting

Other Considerations

- Tetrahydrocannabinol (THC)
  - The active ingredient of marijuana
    - Marketed as dronabinol
    - More effective than placebo in preventing chemotx-induced n/v
    - Mediated by cannabinoid receptors at Vomiting Center in medulla
  - Side effects:
    - Drowsiness, orthostatic hypotension, tachycardia, dry mouth
    - Anxiety, depression, visual hallucinations, and manic psychosis may occur, especially in older individuals and patients who have never used marijuana.
<table>
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<tr>
<th>ANTIEMETIC</th>
<th>INDICATION</th>
<th>SIDE EFFECT / CAUTION</th>
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<tbody>
<tr>
<td><strong>DOPAMINE ANTAGONISTS</strong></td>
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<tr>
<td>Haloperidol 0.5-2 mg po/IV/SQ q 6 h</td>
<td>Toxic/metabolic (e.g. medication-induced, renal, hepatic); for Opioid induced N/V</td>
<td>Dystonia; Sedation; QTc prolongation</td>
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<tr>
<td>Prochlorperazine 5-10 mg po/IV/pr q 8 h</td>
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<tr>
<td><strong>ANTICHOLINERGICS / ANTI-MUSCARINICS</strong></td>
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<tr>
<td>Promethazine 12.5-25 mg po/pr q 4 h</td>
<td>Inflammation of GI tract; Bowel obstruction</td>
<td>Sedation; Delirium Never give IV push</td>
</tr>
<tr>
<td>Scopolamine 1.5 mg patch every 3 days</td>
<td>Prevention of opiate-induced nausea</td>
<td>Sedation</td>
</tr>
<tr>
<td><strong>PRO - MOTILITY ANTAGONISTS</strong></td>
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<tr>
<td>Metoclopramide 5-10 mg po/IV/SQ q 6 h</td>
<td>Gastric stasis</td>
<td>Sedation Caution w/ renal failure</td>
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<tr>
<td><strong>SEROTONIN (5HT3) RECEPTOR ANTAGONISTS</strong></td>
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<tr>
<td>Ondansetron 4 mg po/IV q 6 h</td>
<td>Chemotherapy- or radiation-induced</td>
<td>Mild h/a; Constipation; Caution w/ liver failure</td>
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<tr>
<td><strong>BENZODIAZEPINES</strong></td>
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<tr>
<td>Lorazepam 0.5-1 mg po/IV q 6 h or SL</td>
<td>Anticipatory nausea</td>
<td>Cautions: Weak antiemetic; Avoid as single agent</td>
</tr>
<tr>
<td><strong>STEROIDS</strong></td>
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<tr>
<td>Dexamethasone 8 mg po/IV daily or divided BID</td>
<td>Increased intracranial pressure, nausea refractory to other meds</td>
<td>Mood swings; Elevated BP; Hyperglycemia</td>
</tr>
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