Nausea & Vomiting
Palliative Care Strategies

Chip Baker MS, NP-C, ACHPN
January 2012
“I would like to see the truth clearly before it is too late.”

from *Nausea*

Jean Paul Sartre
Terminology

• **Nausea**: from the Latin naus (ship); a very unpleasant sensation that one may vomit.

• **Retching (dry heaves)**: muscular activity of the abdomen and thorax, often voluntary, leading to forced inspiration against a closed mouth and glottis without oral discharge of gastric contents.

• **Vomiting**: involuntary contractions of the abdominal, thoracic and GI (smooth) muscles leading to forceful expulsion of stomach contents from the mouth.
Terminology

• **Regurgitation**: effortless return of esophageal or gastric contents into the mouth unassociated with nausea or involuntary muscle contractions

• **Rumination**: food that is regurgitated postprandially, re-chewed and then re-swallowed
Epidemiology

- Systemic review of prevalence of symptoms in those with serious illness:
  - Top 3 (consistently >50%): pain, breathlessness, and fatigue
  - Nausea: 16%-68% of patients
    - AIDS 43%
    - ESRD 30%
    - CHF 17%
    - Cancer 6%
Epidemiology

• N&V more prevalent at EOL?
  – N&V found to be a predictor for short survival in one study
  – PC service reported N&V prevalence at various prognoses in 3 other studies
    • >6 months – 36%
    • 1-2 months – 62%
    • Days – 71%
  – N&V peaked with Karnofsky = 40 then decreased in fifth study
Etiology

- GI tract disorders
  - Toxins, infections, obstruction, inflammation, dismotility
- Non-GI infections
  - Liver, CNS, renal, lung, other
- Pregnancy
- Visceral inflammation
  - Pancreas, GB, peritoneum
- Myocardial ischemia or infarction
Etiology

• Other CNS disorders
  – Migraine, neoplasm, bleed
• Vestibular disorders
• Metabolic/endocrine imbalances
  – DKA, uremia, AI, thyroid, parathyroid
• Alcohol tox
• Psychogenic
• Radiation exposure
• Medications
Etiology

• Medications
  – Chemotherapy
  – Analgesics
  – Antibiotics
  – Oral contraceptives
  – Metformin
  – Anti-parkinsonians
  – Anti-convulsants
  – Anti-hypertensives
  – Anesthetic agents
Less common etiologies

- Rapid weight loss/body casts (SMA syndrome)
- Infectious esophagitis
- Opiate withdrawal
- Herbal preparations
Assessment - History

- Quality? nausea, vomiting, retching, projectile
- Duration? persistent versus intermittent.
- Temporal issues? worse in morning?
- Relationship to meals?
- Contents of vomitus?
- Ameliorants/triggers?
- Treatments
- Associated symptoms
  - Pain, fever, myalgias, constipation, diarrhea, vertigo, dizziness, HA, jaundice, weight loss, focal neurological symptoms
Laboratory Studies

- Electrolytes, glucose, BUN/creatinine
- Calcium, albumin, total serum proteins
- CBC
- LFTs
- Pregnancy test
- Urinalysis
- Serum lipase w/ or w/out amylase
Radiological studies

- Plain abdominal films
- Abdominal sono or CT if pain is key feature
- Head CT or MRI if severe HA, papilledema, marked HTN, AMS, or focal neuro findings
- EGD or upper GI
- Gastric emptying studies
Treatment

• ‘The cornerstone of treatment of nausea & vomiting in the Palliative Care patient has been understanding the emetic pathway and the associated neurotransmitters involved in the process.’

Glare P et al, Clinical Interventions in Aging 2011:6
Nausea Pathway

Sensory input (pain, smell, sight) → Higher cortical centres → Memory, fear, anticipation

Chemotherapy → Chemoreceptor Trigger Zone (area Prostema-4th ventricle) → Vomiting Centre (Medulla) → Vomiting Reflex

Chemotherapy → Radiotherapy → Stomach Small intestine

Labyrinths

Neuronal pathways
Factors which can cause nausea & vomiting
Chemo-receptors

Cause - motion
Vestibular input

Cause - biochemical disturbance (e.g., hypercalcaemia)
Chemoreceptor trigger zone

Cause - anxiety or raised intracranial pressure
Higher centres

Receptor-muscarinic cholinergic (AChm)
Histamine type 1 (H1)

Receptor-Dopamine type 2 (D2)
Serotonin type 3 (5HT3)

Receptor-GABA
Histamine type 1 (H1)

VOMITING CENTRE
Receptor-muscarinic cholinergic (AChm)
Histamine type 2 (H2)
Serotonin type 2 (5HT2)

GI TRACT
Receptor-Dopamine type 2 (D2)
Serotonin type 3 (5HT3)

Patient experiences nausea and vomiting

Causes:

- Gastric stasis, intestinal obstruction, gastric irritation
- Patient experiences nausea and vomiting
Treatment Caveat

• This cornerstone may be crumbling:
  – Symptoms may be less common and bothersome than previously estimated
  – The Emetic Pathway was determined to help develop new therapies and may not be relevant in treating PC patients
  – When determining causes for N&V there may be none identified or multiple
  – Neuropharmacology of the pathway is largely redundant
Treatment Caveat

• …crumbling
  – Evidence based research is modest
    • High response rates reported mostly in uncontrolled or case studies
  – Other pathways (cytokines, etc.) may also be involved
  – Interventional gastroenterology and radiology developments increases options for management
Treatment

• Identify and treat underlying cause
• Treat complications
  – Replace losses
• Provide relief of symptoms
  – Empiric versus mechanistic
• Use preventative measures when vomiting is likely to occur
  – S/P chemotherapy, parenteral opiates
Identify underlying causes: six sentinel questions

• Intermittent nausea with early satiety, postprandial fullness or bloating. Nausea is relieved with vomiting small amounts of undigested food indicating impaired gastric emptying.

• Intermittent nausea associated with cramping and altered bowel habit. Nausea relieved with large emesis sometimes bilious/fecal indicating obstruction.
Identify underlying causes: six sentinel questions

- Persistent nausea aggravated by sight/smell of food, unrelieved by vomiting indicating chemical cause.
- Early morning nausea and/or vomiting associated with head ache indicating increased intracranial pressure.
Identify underlying causes: six sentinel questions

- Nausea aggravated by movement (from degrees of turning of head to motion sickness) indicating a vestibular component.
- Nausea and vomiting associated with anxiety indicating a cortical component.
Treat Complications

- Nutritional
- Cutaneous – petechia, purpura
- Oropharyngeal – dental, pharyngitis
- Esophageal – hematoma, inflammation
- GE junctional – M-W tears, Boorhaave’s rupture
- Renal – prerenal azotemia, ATN, hypokalemic nephropathy
- Metabolic – electrolytes, acid-base, water
Treat Complications: Metabolic

- **Alkalosis**
  - Retention of HCO3 and volume contraction

- **Hypokalemia**
  - Renal K loss, GI K loss, reduced intake K loss
  - Note: those with uremia or Addison’s may have normal or even high K despite vomiting

- **Hypochloremia**
  - GI chloride losses

- **Hyponatremia**
  - Free water retention 2/2 volume contraction
Symptom Relief - evidence

- Systematic review-studies of anti-emetics used in advanced cancer (Glare P. et al Support Care Cancer 2004 Jun 12(6))
  - Total 21: highly selective population(s) ➔ no heterogeneity
    - 2 systematic reviews
    - 7 RCT
      - Response rate 23-36% nausea; 18-52% vomiting
    - 12 uncontrolled studies/case series
      - Response rate 75-93% nausea and vomiting
    - Mechanistic versus empiric method both equally effective
    - Strong evidence for metoclopramide in cancer-associated dyspepsia; steroids in malignant BO
    - Conflicting evidence about seratonin antagonists versus standard txs e.g. metoclopramide, dopamine antagonists
    - Little to no evidence on efficacy of some commonly used drugs: haloperidol, cyclizine, methotrimeprazine
# Symptom relief

## Antiemetic receptor site affinities

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dopamine antagonist</th>
<th>Histamine antagonist</th>
<th>Acetylcholine muscarinic) antagonist</th>
<th>Serotonin type 2 antagonist</th>
<th>Serotonin type 3 antagonist</th>
<th>Serotonin type 4 antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclizine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyoscine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levomepromazine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoclopramide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ondansetron</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Promethazine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Symptom relief - Prokinetics

- **Mechanism**
  - Activates 5HT4 receptors - releases acetylcholine
  - Blockade of 5HT3 receptors
  - Activates motilin receptors
  - Releases dopiminergetic brake on gastric emptying

- **Contraindicated** – obstruction; post surgery

- **Interactions** – antimuscarinic agents (antihistamines)

- **Metoclopramide** – works on stomach and proximal small bowel, not colon
  - 3 small placebo-controlled trials w/mixed results
  - 10mg TID-AC (RI: 5mg TID-AC/ESRD: 2.5mg TID-AC)
  - SE: restlessness, somnolence, fatigue, EPS (>12 weeks)

- **Mirtazipine; erythromycin**
Symptom relief – Dopamine antagonists

• Broad spectrum of activity
  – Block many receptors
  – May have prokinetic effects thru vagal blockade in the GI tract

• Prochlorperazine
  – 5-10mg tid-qid (PO and IV)
  – 25mg bid-tid rectally
  – Dose reduction in elderly and liver disease
  – SE: neutropenia (watch ANC<1000), confusion, resp depression, EPS, anticholinergic effects
  – No trials in advanced cancer. Less effective than metoclopramide for chemo-induced nausea
Symptom relief – Dopamine antagonists

• Haloperidol
  – No randomized controlled trials evaluating haloperidol for N&V
    • 0.5mg IV/SQ q4-6hr
  – ABHR ((lorazepam, diphenhydramine, haloperidol (gel:1-2mg, suppository: 0.25-1mg), metoclopramide)
    • No prospective studies
    • Topically q6hr
  – Dose reduce for liver disease
  – Avoid with Parkinson’s disease
  – SE: less sedation; less hypotension; more EPS
Symptom relief – Dopamine antagonists

• Chlorpromazine
  – More sedating
  – Large randomize trial for empiric tx of nausea established efficacy only 20-30% of the time

• Olanzepine
  – SE: less EPS; but, anticholinergic effects, somnolence, increased appetite
  – 2 small subjective cases were positive
Symptom relief - Antihistamines

• Work at the vomiting center and chemoreceptor trigger zone
  – Reduces mucosal secretory activity (antimuscarinic)
    • BO

• Promethazine
  – 25mg PO/IV q4-6hours (max 100mg daily)
  – Dose 12.5mg if SE limiting
  – SE: sedation, dizziness, EPS, HA, constipation, urinary retention, lowered seizure threshold, confusion
  – No studies
Symptom relief - Antihistamines

• Diphenhydramine, hydroxyzine, meclizine, cyclizine
  – More muscarinic > usefulness in bowel obstruction - cyclizine
  – Significant SE: watch elderly
  – One uncontrolled study of mechanistic approach showed 5-10% cases treated with cyclizine successfully
Symptom relief – Selective 5HT3 receptor antagonists

• Effects receptors centrally and in periphery
  – Sit on vagus nerve that feeds emetic center; cells of the peripheral enteric nervous system; nucleus tractus of chemoreceptor trigger zone
  – Block effect of serotonin on vagus nerve
  – Used manly in chemo induced nausea
  – For PC pts reserved as third-line for refractory nausea cases
  – Effective in bowel obstruction and renal dx which are associated with > serotonin release
Symptom relief – Selective 5HT3 receptor antagonists

- Ondansetron (granisetron, tropisetron, dolasetron, palonosetron)
  - 4-8mg QD or BID
    - Liver disease: maximum 8mg daily
  - IV, PO, SL; Transdermal granisetron (Europe); PO film in trials
  - SE: minimal; constipation 5-10% of patients
    - Watch QT interval; contraindicated in those at risk for torsades
    - Reduces tramadol efficacy
  - Many favorable studies used as prophylactic
  - 2 Randomized controlled trials in advanced cancer
    - Tropisetron >effective than metoclopramide or chlorpromazine
    - No sig difference in ondansetron, metoclopramide and placebo for opioid-induced nausea
- Uncontrolled case series
  - Ondansetron as second-line agent was effective in 80% of pts
Symptom relief - Corticosteroids

- Act centrally, but primary action unknown:
  - Reduction of BBB permeability to toxins
  - Inhibition of enkephalin release in brainstem
  - Depletion of GABA stores in medulla
- Studies have shown efficacy rates of <20% to 75%
  - Bowel obstruction
  - Chemo-induced nausea
  - Raised intracranial pressure
  - Second-line for chronic nausea
- SEs: hiccups
- Dexamethasone
  - 4-8mg daily (nausea); otherwise up to 16mg daily (BO)
Symptom relief - Benzos

• Minimally effective
  – May reduce anticipatory emesis
  – Sedation may allow temporary relief

• Lorazepam
  – Short acting
  – Inactive metabolites
Symptom relief - Scopolomine

• Pure anticholinergic agent
  – Relax smooth muscles
  – Reduces GI secretions
• SE: typical of anticholinergics
Symptom relief - Octreotide

• Somatostatin analogue
  – Refractory bowel obstruction
  – Reduces secretions from bowel and pancreas
  – Reduces GI motility
  – Causes vasoconstriction
  – Analgesic effects: partial mu-opioid agonist
  – 100mcg SQ tid or 100-600mcg IV daily
  – SE: skin reaction, cramps, N&V, diarrhea, constipation, gallstones, HA, bradycardia, QT prolongation
  – Caution: DM, RF, endocrinopathies, hepatic dx
Symptom relief - Cannabinoids

• Effects CB1 receptors in brain (unknown if they are found in structures of emetic pathway)
• Effects are short in duration
• CNS depressant effects
Symptom relief – Non-pharm

• Diet restrictions
  – Avoid fatty, spicy, highly salty foods

• Behavioral approaches
  – Distraction, relaxation, guided imagery,

• Massage
  – Foot massage

• Acupuncture
  – Studies show effectiveness on chemo-induced nausea and anticipatory nausea
Symptom relief – Nonsurgical procedures

• Advanced cancer – 3% present with BO
  – Bowel CA and Ovarian CA lead the way
• PEG - success rate for placement – 89-100%
  – Complications: ascites/leakage 9%; infection; obstruction; bleeding; tube obstruction; tube migration
  – Small study 64% reported improvement of nausea, vomiting, insomnia, mood, weakness and concentration after 7 days (symptom distress scale)
• NGT – short term
  – SE: poor tolerance; restriction in activity; pain; altered body image
  – complications: aspiration; hemorrhage; gastric erosion; alar necrosis; sinusitis; otitis
• Stents
• Colonic decompression tube
Psychogenic Vomiting

- Usually young and female
- Denial or minimization of nausea
- Rarely occurs in public or in front of others
- Co-existing eating disorder, laxative abuse, diuretic abuse
- Psychological disturbances common
- Complications may be present
Resources


Resources

- Saskie D et al, Droperidol for treatment of nausea and vomiting in palliative care patients, *Cochrane Database of Systematic Reviews*, 2010; issue 10