NAUSEA AND VOMITING

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Background

- Nausea: inclination to vomit; awareness that vomiting is imminent
- Vomiting: forceful expulsion of gastric content
  - Nausea → retching → vomiting
- Emesis is often associated with symptoms of pallor, tachycardia, and diaphoresis
- N/V could be isolated or part of complex clinical picture
- N/V can be debilitating in some cases

Etiology

- Chemotherapy, radiation therapy, anticipatory
- GI obstructions, infections, inflammations
- Motion sickness, vestibular disorders
- ICH, meningitis, migraine
- Pregnancy, post-operative, noxious odors
- Psychogenic (bulimia and anorexia nervosa)
- AMI, CHF, DKA, uremia
- Drug withdrawal (opiates, benzos)
- Opioids, hormone therapy, anticonvulsants
- Digoxin and theopylline: dose-dependent

Pathophysiology

- Sensory centers send impulses to vomiting center in the medulla
  - Chemoreceptor trigger zone (CTZ) (5-HT_3, D_2, NK_1)
  - Cerebral cortex (sights, smells, emotions..)
  - GI (5-HT_3, D_2, NK_1)
  - Vestibular system (H_1, muscarinic)
- Vomiting centers integrates information and triggers a coordinated sequence of N/V
- CTZ is major chemosensory organ often associated with chemically-induced vomiting and pregnancy-induced vomiting

Presentation

- Simple vs. Complex
- Serious consequences include weight loss, electrolyte imbalance, dehydration, esophageal perforation
- Lab: related to dehydration and lytes

Treatment

- With simple N/V treatment is often unnecessary
- With complex N/V symptoms may never completely go away
- Identify underlying cause, hydrate and correct lytes if necessary, determine PO tolerance to medications
- Non-pharmacologic therapy
  - Dietary: ginger, small frequent meals, bland foods..
  - Physical: acupuncture
  - Psychological: hypnosis, psychotherapy

Pharmacologic Therapy

- Based on targeting the various chemoreceptors (5-HT_3, D_2, NK_1, H_1, muscarinic)
- Factors to consider: success of previous therapy, route (IV/rectal/PO/transdermal), etiology, frequency and severity of episodes

Pharmacologic Therapy
Serotonin (5-HT_3) Receptor Antagonists

- Ondansetron (Zofran), etc.
- Serotonin released 2/2 chemotherapy
- 5-HT_3 RAs block receptors in GI and inhibit acute phase of CINV
- Standard of care in management of CINV, PONV, RINV
- All agents are considered equally effective and safe, IV and PO
- AEs: well tolerated, constipation, headache

Pharmacologic Therapy
Anticholinergics-Antihistamines

- Block receptors in vestibular system
- Anticholinergics
  - Scopolamine transdermal patch, 1.5 mg Q72h
  - Effective for preventing and treating PONV and motion sickness N/V
- Antihistamines
  - Dimenhydrinate (Dramamine), diphenhydramine, meclizine
  - Effective for preventing and treating motion sickness and vertigo associated N/V
  - 2nd generation not effective (fexofenadine, cetirizine)

Pharmacologic Therapy
Dopamine Antagonists

- D_2 receptor antagonists (CTZ, GI)

1. Phenothiazines
   - Promethazine (Phenergan), prochlorperazine (Compazine), chlorpromazine (Thorazine)
   - Available PO/IV/PR
   - Effective for N/V treatment in severe motion sickness or vertigo, gastritis/gastroenteritis, PONV, CINV, NVP
   - AEs: sedation, EPS with chronic use

Pharmacologic Therapy
Dopamine Antagonists

2. Droperidol, Haloperidol (Haldol)
   - Typical antipsychotics
   - Effective in preventing PONV and treating opioid-induced N/V
   - Use reserved for complex N/V or as 2nd line agent
   - AEs: sedation, QT-prolongation (Black Box warning for droperidol)
3. Metoclopramide
   - Central and peripheral mechanisms
   - Cholinergic activity → promotes gastric motility
   - Effective for PONV, CINV, NVP
   - AEs: EPS, hyperprolactinemia, gynecomastia

Pharmacologic Therapy
Corticosteroids

- *Dexamethasone*, methylprednisolone
- Unknown MOA
- CINV, PONV, RINV
- More effective in prevention than treatment of CINV
- Use for complex N/V only

Pharmacologic Therapy
Cannabinoids

- 2nd line agents for CINV
- Complex central effects
- Dronabinol and nabilone
- AEs: sedation, euphoria

Pharmacologic Therapy
Benzodiazepines

- Lorazepam, alprazolam
- Effective in anticipatory N/V
- May inhibit impulses from cerebral cortex to vomiting center
- Used to prevent anxiety or N/V in pts receiving highly ematogenic chemotherapy
- AEs: resp. depression, sedation

Pharmacologic Therapy
Neurokinin-1 (NK_1) Receptor Antagonists

- NK_1 receptors are found in GIT and brain
- Aprepitant → substance P/NK_1 RA
- Effective for prevention of acute and delayed phases of CINV
- AEs: serious drug-drug intxns (CYP3A4 inhibitor)

CINV

- CINV: Acute (< 24h), delayed (> 24h), anticipatory
- Ematogenic potential of chemo agents: Minimal (< 10% risk), low (10-30%), moderate (30-90%), high (>90%)
- Prophylaxis of acute CINV
  - Low ematogenic potential: single agent is effective (dexamethasone, metoclopramide, prochlorperazine, lorazepam) on day of chemo
  - Moderate ematogenic potential: two antiemetic drug combination (5-HT_3 RAs, dexamethsone) on day of chemo
  - High ematogenic potential: 3 antiemetic drug combination given on day of chemo (5-HT_3 RAs, dexamethsone, NK_1 RA) on day of chemo

CINV

- Prophylaxis for delayed CINV is more difficult
  - Most common with cisplatin- and cyclophosphamide-based regimens
- Best to control acute CINV and provide adequate prophylaxis for delayed CINV
- Aprepitant, dexamethasone, metoclopramide are effective in delayed CINV
- Agents may be combined
- Agents with different MOA may be used for breakthrough N/V

PONV

- Incidence up to 30% in pts post-anesthesia
- Occurrence within 24h of anesthesia, most common within 2h
- Risk factors: female gender, non-smoking status, history of PONV or motion sickness, opioid use, anesthetic factors, surgical factors
- Pts with high risk warrant prophylaxis
  - 5-HT_3 RAs (and/or droperidol) at end of procedure
  - Dexamethasone dose prior to induction
  - Antihistamines/anticholinergics may be effective
  - Very high risk pts should combine two agents, otherwise a single agent is sufficient

PONV

- All non-high-risk surgical pts should have PRN standing orders for 5-HT_3 RAs (and/or droperidol)
- Aprepitant is approved for PONV prophylaxis when given within 3h prior to induction
- Droperidol is very effective but use is limited
- Breakthrough N/V should be treated with an agent of different MOA, i.e. phenothiazine, metoclopramide, or droperidol
- Acute PONV without prophylaxis should be treated with 5-HT_3 RAs as first line (2^{nd} line = dexamethasone or droperidol or phenothiazine)

NVP

- Up to 75% of pregnant woman experience N/V during 1^{st} trimester
  - Usually self-limited
  - 1-3% develop hyperemesis gravidarum
- Poorly understood mechanism
- Risk of teratogenicity must be weighed
- Trial of non-pharmacologic therapy
- Pyridoxine (Vit B6) 10-25 mg 1-4x/d with or without doxylamine 12.5-20 mg 1-4x/d is 1^{st} line therapy
- More severe NVP may require promethazine, prochlorperazine, metoclopramide, ondansetron

NVP

- Hyperemesis gravidarum requires hospitalization
- IV fluid replacement
- Parenteral nutrition may be given for weight loss
- Ondansetron may be tried
- IV Methylprednisolone may be considered as last resort
  - Risk of oral cleft in fetus during first trimester use

Motion Sickness and Vestibular

- Vestibular disturbances: infections, traumatic injury, neoplasm, motion..
- Anticholinergics/antihistamines are 1^{st} line Rx
- Precise MOA not well understood
- Best if administered prior to motion
- Scopolamine patch is preferred for motion sickness 2/2 convenience, but not superior to antihistamines