Managing Dyspnea, Nausea, and Thirst in the Hospitalized Patient

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Objectives

- Recognize the prevalence and impact of common non-pain symptoms in patients with serious illness
- Master best practices for evaluating and treating such symptoms
- Understand the evidence base for recommended symptom management strategies in palliative care

Disclosures

- No relevant disclosures
Interactive Polling Will Be Used Today!

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A 47 year old woman with a severe dilated cardiomyopathy is on home hospice, ineligible for transplantation or a VAD. She is hospitalized for severe dyspnea. Her resting and ambulatory oxygen sats are 96 and 92%, respectively. Cardiology notes indicate she is on maximal medical HF therapy, including aggressive diuretic regimen. Pulmonary edema appears unchanged compared to prior. The patient requests home oxygen therapy upon DC to help alleviate her breathlessness. The next best step is to:

A. Order home oxygen therapy for the patient
B. Initiate lorazepam PRN for dyspnea
C. Recommend use of a hand-held fan and PRN morphine for her dyspnea
D. Request that the patient see her cardiologist for further optimization of her heart failure meds
Dyspnea is a subjective experience that has several components

“Subjective experience of difficult or distressed breathing”

Qualitative studies demonstrate 3 components:
- Air Hunger (unpleasant sensation of the need to breathe, but unable to increase ventilation)
- Effort of Breathing (physical discomfort and fatigue associated with breathing)
- Chest Tightness (feeling of constriction, inability to inhale fully)

Dyspnea is prevalent and multi-factorial in serious illness

- Dyspnea is common:
  - Up to 70% of cancer patients
  - 88-91% of ESLD patients
  - >60% of dying CHF patients
  - Up to 46% of ESRD patients
  - Up to 62% of AIDS pts
- Dyspnea is exacerbated by physical deconditioning and cachexia, and worsens during the dying process
Dyspnea can occur in the absence of lung disease, and pathophysiology is complex

- Dyspnea can occur without primary lung pathology and does NOT always correlate with hypoxemia
- Pathophysiology is complex and incompletely understood
- Similar to pain: physical phenomenon but sensory experience
- Self-report is the gold standard for assessment: use a 0-10 scale

Anxiety can exacerbate dyspnea and fuel a cause and effect spiral

- Objective findings (hypoxemia and hypercarbia) may not correlate with dyspnea

Diagnostic evaluation of dyspnea in serious illness depends on goals of care

- Best treatment of dyspnea is treatment of underlying cause, but extensive workup may not be feasible or warranted in the seriously ill
- Diagnostic evaluation should be individualized, considering prognosis and goals of care
- Focus should be on:
  - Identifying easily reversible causes
  - Symptom management
Use specific disease-modifying therapies depending on the underlying etiology

**Glucocorticoids**
- Bronchospasm
- Lymphangitic spread
- Radiation pneumonitis

**Bronchodilators**
- Bronchospasm and cough

**Diuretics**
- Volume overload

**Thoracentesis/PleurX catheter**
- Malignant pleural effusions

Opioids are the gold standard for refractory dyspnea
- Opioids can be highly effective in alleviating dyspnea, with multiple possible mechanisms of action
  - Decreased central perception of dyspnea
  - Decreased sensitivity to hypercapnia
  - Decreased associated anxiety
- Multiple RCTs, systematic reviews and meta-analyses show benefit

Use lowest effective dose of short-acting opioids for acute symptom relief
- Generally start with low-dose short-acting opioids initially:
  - Oral morphine 2-5mg q3-4hrs PRN
  - Oxycodone 2.5-5mg q3-4hrs PRN
- If needing more immediate relief, can use parenteral opioids
- Boluses are better than infusions for acute symptoms
Data does not support the use of nebulized opioids or furosemide for dyspnea

- Nebulized opioids: local, rapid dyspnea relief, less side effects?
  - Several RCTs: nebulized opioids are no better than saline
  - Systematic reviews show no benefit
- Nebulized furosemide: reducing dyspnea through lung mechanisms?
  - Uncontrolled trials suggest benefit
  - One controlled trial: no better than saline control

Benzodiazepines should only be used if significant anxiety accompanies dyspnea

- Benzodiazepines target anxiety component of dyspnea
- Cochrane Review 2016: no significant effect on dyspnea for COPD or cancer patients
- Benzos should be considered 2nd or 3rd line after opioids and non-pharmacologic treatment
- Weigh risks of delirium/AMS

Non-pharmacologic treatment of dyspnea: evidence for some, not for others

- Supplemental oxygen is only helpful in hypoxic patients
- Bedside fan (air movement) has been shown to be helpful
- Behavioral therapies: sitting upright, pursed lip breathing, relaxation, pulmonary rehab
- Environmental modifications
- Acupuncture
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Back to our case

Case, continued

When offered low-dose oral morphine elixir for breathlessness, the patient becomes upset, as she’s heard that opioids “cause you to stop breathing”. An appropriate response is:

A. Gently explain that when opioids are used appropriately for such symptoms, the risk of respiratory depression is exceedingly low
B. Send her home with an accompanying naloxone order
C. Suggest a change to oxycodone, as this is less likely to induce respiratory depression
D. Compromise by offering a trial of steroids for dyspnea before revisiting opioids
When used appropriately, opioids are safe

- Multiple RCTs: no SAEs, no adverse effects on ABGs or O2 sats, no significant respiratory depression
- ACCP recommends using opioids for refractory dyspnea in patients with advanced cardiopulmonary disease
- Use lowest effective opioid dose
- Principal of double effect

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Another case

You are called to the bedside of a 94 year old man with end-stage dementia and colon cancer, whose care is now comfort-focused. He has had no oral intake in days and is actively dying. He has a history of delirium from medications. His family is distressed by the increasing oral secretions and gurgling. They ask you to do something to manage this upsetting symptom. Which of the following is the best option to manage his secretions while minimizing the risk of delirium?

A. Glycopyrrolate
B. Hyoscyamine
C. Scopolamine
D. Atropine ophthalmic solution
E. Oral suctioning as needed
Ability to swallow and cough/gag reflex diminish → saliva pools in the posterior oropharynx and upper airway → gurgling and rattling (“death rattle”) → 25-50% of dying patients

Often most distressing for family/providers → reassurance is key

Poor prognostic indicator (median time to death ~16 hrs)

Terminal secretions are common at EOL and a reliable predictor of near death

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  - 25-50% of dying patients
- Often most distressing for family/providers → reassurance is key
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Management of terminal secretions

- Reposition for postural drainage, elevate HOB
- Avoid suctioning
- Anti-cholinergics
  - Atropine, levain, scopolamine all equally effective but have risk of CNS anti-cholinergic effects
  - Glycopyrrolate (IV or nebulized) less likely to cross BBB, so less deliriogenic
  - Scopolamine patch is long-acting and may take 12-24hrs to peak
Back to our case

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Nausea

A 51-year-old woman with end-stage renal disease elected to stop dialysis five days ago. She has become more nauseated each day. The nausea is most likely to be alleviated by administration of an antiemetic drug that acts at which of the following anatomic areas?

A. Cerebral cortex
B. Vestibular nucleus
C. Chemoreceptor trigger zone
D. Gastrointestinal tract

Another case
Nausea and vomiting is a significant clinical problem in serious illness

- Nausea is highly prevalent:
  - 70-80% of patients on chemotherapy
  - 62% of all cancer patients, 40% in the last 6 weeks of life
  - 25% of pain consults
- Often undertreated: only 39% hospitalized cancer patients receive anti-emetics
- Negative emotional/QOL impact, with similar distress levels to pain
- Associated with shortened survival

Nausea is caused by one of four pathways acting on the vomiting center

Nausea: “Subjective sensation that precedes vomiting”

“Nauseous” v “Nauseated”

Caused by stimulation of 1 of 4 sites acting on the Vomiting Center (nucleus of tractus solitarius and reticular formation of the medulla)
Nausea is caused by stimulation of 4 sites

Vomiting: “Forceful expulsion of gastric contents by a complex neuromuscular process with voluntary and involuntary components”
Aka, to: “Yak, Upchuck, Barf, Retch, Raff, Hurf, Spew, Blowy, Puke, Chunder, Vom, One’s Cookees, Worship the Porcelain God…”

- Vomiting center = final common pathway → parasympathetic and motor-efferent activity → vomiting
- By whatever name, understanding mechanism is key to effective therapy

There are many possible causes of nausea and vomiting in seriously ill patients

Chemotherapy
Radiation
Medications: opioids, antibiotics, antidepressants, iron, potassium
Infection (especially gram negatives)
Gastritis/PUD
Dysmotility/Gastroparesis/Peritonial Compression/Acute Obstruction
Pancreatitis
Graft vs host disease
Metabolic abnormalities: e.g. hypercalcemia
Uremia
Brain metastases
Anxiety
Oropharyngeal Secretions/Mucositis/Thrush
Anticipatory nausea
And on and on….

Careful assessment leads to simplification of differential
Diagnostic evaluation of nausea in serious illness depends on goals of care

- Diagnostic evaluation should be individualized, considering prognosis and goals of care
- Cause can be found in ~75% of terminally ill patients
  - Most common causes:
    - impaired gastric emptying (44%)
    - chemical/metabolic/infectious (33%)
    - visceral/bowel (31%)
- History and physical is the most important aspect of the diagnostic evaluation
  - Labs and imaging only if appropriate/desired

Careful history helps focus differential

N: nausea intensity (0-10), duration, description
A: alleviating factors
U: usual pattern of occurrence (time, post-prandial, activities)
S: symptoms associated w/ N/V (vertigo, HA, fever, anxiety, pain, constipation, etc.)
E: exacerbating factors
A: anti-emetic history (prior meds and effect)

A mechanistic approach to nausea and vomiting is better than a "shotgun" approach

- Recommend mechanism-based therapy:
  - After H&P, use knowledge of pathophysiology to create a differential
  - Treat underlying etiology and chose antiemetic that blocks implicated receptors
  - Don’t just treat the symptom!
Careful assessment leads to identification of pathway to target:

**Chemical/Metabolic**
- Chemotherapy Related: Serotonergic, NK, Dopamine
- XRT Related: Serotonergic
- "Toxic" Opioid/Med/Infection: Dopamine mediated
- Electrolyte Imbalances (Ca+, Uremia): Dopamine mediated

**CNS/Cognitive**
- Brain Mass/Increased ICP: Inflammation/Cytokine, Histamine
- Vestibular: Ach, Histamine
- Anxiety/Anticipatory Nausea: Cortical effect

**Abdominal/Visceral**
- GERD/PUD: Acid/Inflammation, Vagal Input
- Constipation
- Dysmotility
- Ileus
- Malignant Bowel Obstruction

Knowledge of anti-emetic receptor activity leads to targeted therapy:

**Pure Antagonists**
- Receptor: Drug
- D2 (central): Haloperidol
- H1: Diphenhydramine, Ach: Scopolamine
- 5HT3: Ondansetron, NK1: Aprepitant

**Mixed Antagonists**
- Receptors: Drug
- D2 > H1 > Ach: Compazine
- H1 > Ach > D2: Phenergan
- 5HT2 > D2 > H1: Olanzapine

**Others**
- Site of Action: Drug
- Corticosteroids
- Anticipatory anxiety: Cognitive Behavioral
- Pain: Benzodiazepines
- Drugs (Chemotherapy, Opioids)
- Metabolic derangements
- 5HT3 Antagonists
- Metoclopromide
- Bowel Regimen
- Decompressive therapies
- Steroids, octreotide
- Irritation/injury
- Dysmotility
- Constipation
- Obstruction

Understanding mechanism is key to targeted N/V therapy:

**Vestibular Center**
- Motion sickness
- Antihistamines (H1): Scopolamine

**GI Causes**
- 5HT3 Antagonists
- Inflammation/injury: Proton Pump Inhibitors

**Intracranial Pressure**
- Meningeal irritation

**Chemoreceptor Trigger Zone**
- Intracranial injury: Corticosteroids
- 5HT3 Antagonists
- NK-1 inhibitors
Practical pearls for pharmacologic management of nausea and vomiting

- **Dopamine blockers are often first line** given most common etiologies; all have risk of EPS
  - Haloperidol is the most potent D2 antagonist available and is a highly effective anti-emetic
- Ondansetron is good for CINV, but is constipating: use caution
- Scheduled/around-the-clock medications are more effective than PRN
- Benzodiazepines should be reserved for clear anticipatory N/V given risk of delirium, sedation


Remember non-pharmacologic management strategies for nausea and vomiting

- Avoid strong smells or other triggers
- Small, frequent meals
- Limit oral intake during severe episodes
- Relaxation techniques
- Acupuncture and acupressure


Acupuncture

Cochrane Meta-analysis of 11 pooled RCTs w/ 1,247 pts\(^1\)
- Reduction in risk of acute emesis (RR=0.82) but not acute or delayed nausea

RCT of 104 breast Ca pts comparing electroacupuncture v needles alone v standard anti-emetic meds over 5 d period in JAMA 2000\(^2\)
- Electroacupuncture: ~ 5 episodes
- Needles alone: ~10 episodes
- Standard meds: ~15 episodes
  *Statistically significant
- Acupuncture not incorporated into ASCO or NCCN guidelines

\(^1\) Ezzo et al. Acupuncture-point stimulation for chemotherapy-induced nausea or vomiting. Cochrane Data Syst Rev 2, 2006
Refractory nausea: what if nothing is working?

If initial agent isn’t helping:
1. Re-evaluate for alternate causes (head CT, EGD, etc.)
2. Increase/optimize dose of selected agent
3. Rotate to different agent within same class
4. Consider dexamethasone, ondansetron, aprepitant
5. If above ineffective, consider haloperidol, olanzapine, or cannabinoids

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Back to our case
A middle aged man with end-stage cancer is actively dying in the hospital, receiving comfort-focused care. He is obtunded, his mouth is dry, but he has anasarca and ascites. His partner is distressed because the patient stopped eating and drinking a few days ago, and he perceives the patient to be suffering from thirst and "dehydration". He asks you to start IV fluids. The best response is:

A. Start IV fluids at 125cc/hr
B. Express concern that this will contribute to discomfort from fluid retention, and offer intensive mouth cares, swabs, and lip moisturizer
C. Start IV fluids, but only TKO
D. Reassure that most dying patients don’t experience thirst

Another case

Thirst is a subjective experience influenced by many factors

- Thirst is the desire to drink fluids in response to a water deficit
- Cues to drink include:
  - Social customs
  - Dry mouth
  - Accompanying food intake
  - Fluid availability
  - Palatability
Patients with serious illness have multiple risk factors for thirst

- Dehydration
- Electrolyte disturbances
- Hypotension
- Dry mouth
- Immobility → inability to access fluid
- Imposed fluid restrictions
- Medications
- Mechanical ventilation
- Heart failure
- Renal failure

Thirst is prevalent and highly distressing in serious illness

- Thirst is extremely common:
  - 80-90% of dying patients
  - >70% of critically ill ICU patients
- Distress from thirst is high
  - In one ICU study, it was the MOST distressing symptom

Separating thirst from dry mouth can be difficult, and affects our evaluation

- Thirst does not always correlate with xerostomia
- Dry mouth used as surrogate marker, so true prevalence and treatment effects unclear
- Self-report is best: assess dry mouth and thirst independently
- Evaluation should include H&P (including volume status and oral exam), medication review, ?electrolytes

Puntillo, 2010
Puntillo, 2014
Managing thirst in special populations

- ICU patients
  - RCT, >250 patients: "ICU bundle" of oral swab wipes, sterile ice-cold water sprays, and a lip moisturizer decreased thirst intensity, distress and dry mouth
- Dying patients
  - Artificial hydration is controversial
  - Most studies show hydration doesn’t improve thirst
  - Offer daily oral care, sips and swabs

B. Express concern that this will contribute to discomfort from fluid retention, and offer intensive mouth cares, swabs, and lip moisturizer

Managing thirst in special populations

- ESRD patients on dialysis
  - Thirst associated with higher inter-dialytic weight gain (IWG)
  - Daily dialysis reduces thirst scores, but is impractical
  - ACEIs reduce thirst, but effect fades after 6 months
  - Frequent gum chewing and saliva substitute may help
- Heart failure patients
  - Liberalizing fluid restrictions decreases thirst (in stable and decompensated HF) with no change in mortality or readmissions
  - Always discuss fluid liberalization with cardiologist

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Thank You!
Questions?