Management of Common Non-Pain Symptoms in Palliative Care

Bethany-Rose Daubman, MD
Cindy Lien, MD
Practical Aspects of Palliative Care
September 2017

- No conflicts of interest to disclose

Common Non-Pain Symptoms in Palliative Care

- Nausea/ vomiting
- Fatigue
- Dyspnea
- Malignant bowel obstruction
The Case of Mr. B

- 49 yo M w/ advanced colon cancer, progressed through chemo, waiting to enroll in a trial, admitted for N/V
- Nausea worse with movement/ingestion of big pills
- Vomiting daily after meals x1 week
- Emesis is partially digested food
- + heartburn, + odynophagia
- - fevers, headaches, focal weakness
- Denies constipation, but wife says his last BM was 1 week ago
- PMHx: DM2 (x9 years), depression, insomnia

Symptom Management Model

- Assess
- Differential Diagnosis
- Plan
- Intervene
- Evaluate
Mr. B’s Medications

- Med List:
  - Ondansetron 4mg IV q6 PRN (given ATC)
  - Prochlorperazine 10mg IV q6 PRN (x 2 doses in 24h)
  - Lorazepam 1mg SL q4 PRN (x 1 in 24h)
  - Docusate 100mg BID
  - Amitriptyline 50mg QHS
  - Omeprazole 20mg qd
  - Fentanyl 150mcg/hr TD patch
  - MOM PRN (x 1 dose in 24h)

Mr. B’s Exam

- VS: afebrile, HR 105

- Exam:
  - Gen: thin, ill-appearing
  - HEENT: white plaques on hard palate, dry MM
  - ABD: scaphoid, quiet BS, diffuse mild tenderness to palpation

Mr. B’s Labs & Studies

- K = 2.8
- BUN/Cr = 72/2.3 (baseline 23/1.4)
- LFTs and CBC wnl

- CT A/P (2 days PTA): diffuse gastric wall thickening, minimal ascites, peritoneal carcinomatosis, significant retained stool
Nausea and Vomiting in Palliative Care

- 40% prevalence in last 6 weeks of life
- Common in cancer, CHF, AIDS
- Often part of symptom cluster (e.g. pain)
- Provokes distress and fears about:
  - Starvation
  - Dehydration
  - Disease progression
  - Loss of control and dignity

Complications of Nausea and Vomiting

- Dehydration
- Electrolyte imbalances
- Malnutrition
- Aspiration risk
- Mallory-Weiss tears
- Anticipatory and refractory N/V
- Depression
- Withdrawal from therapy
- Suffering

Systematic Approach to Nausea

- Need a provisional nausea/vomiting dx
  
  What is the probable etiology?
  - Know the relevant neuroanatomy and locations of receptors
  - Determine responsible pathophysiologic mechanism(s)
  - Choose targeted agents that block the relevant receptors and factor in the pathophysiology
  - Must address and treat the non-physical aspects as part of standard evaluation
### A differential for nausea

- **V** estibular/Vertigo
- **O** bstruction/Obstipation
- **M** otility dysfunction
- **I** nflamation/Infection
- **T** oxins/Medications
- **N** erves
- **G** ums/Oropharynx

---

### Credit where credit is due...

and a little bragging!

![Palliative Care Fast Facts](http://www.mypcnnow.org/fast-facts)

- Peer-reviewed, evidence based summaries of Palliative care topics
- Palliative Care Fast Facts app - free

http://www.mypcnnow.org/fast-facts

---

<table>
<thead>
<tr>
<th>Vestibular/Vertigo</th>
<th>Labyrinthitis</th>
<th>Vestibular nerve involvement by tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstruction/Obstipation</td>
<td>Adhesions</td>
<td>Constipation</td>
</tr>
<tr>
<td>M otility Dysfunction</td>
<td>Autonomic dysfunction</td>
<td>Ascites</td>
</tr>
<tr>
<td>Inflammation/Infection of gut</td>
<td>Chemo XRT</td>
<td>Gastitis PUD</td>
</tr>
<tr>
<td>Toxins/Medications</td>
<td>Urnia, ↑Ca, ↓Na</td>
<td>Mucooeicls Antibiotics Anticholinergics</td>
</tr>
<tr>
<td>Intracranial</td>
<td>Increased ICP</td>
<td>Meningeal irritation</td>
</tr>
<tr>
<td>N erves</td>
<td>Anxiety, Depression</td>
<td>Anticipatory nausea, Pain</td>
</tr>
<tr>
<td>G ums/Mouth/Oropharynx</td>
<td>Mucositis</td>
<td>Oral HSV</td>
</tr>
</tbody>
</table>

http://www.mypcnnow.org/fast-facts
### Pathophysiology of nausea and vomiting

<table>
<thead>
<tr>
<th>Vestibular/Vertigo</th>
<th>Ach</th>
<th>( H_1 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstruction/Obstipation</td>
<td>Multiple receptors</td>
<td></td>
</tr>
<tr>
<td>Mobility Dysfunction</td>
<td>( D_2 ) (peripheral)</td>
<td></td>
</tr>
<tr>
<td>Inflammation/Infection of gut</td>
<td>( SHT_3 )</td>
<td></td>
</tr>
<tr>
<td>Toxins/Medications</td>
<td>( D_2 ) (central) ( NK )</td>
<td></td>
</tr>
<tr>
<td>Intracranial</td>
<td>Ach ( H_1 ) ( SHT_2 )</td>
<td></td>
</tr>
<tr>
<td>Nerves</td>
<td>Cortical</td>
<td></td>
</tr>
<tr>
<td>Gums/Mouth/Oropharynx</td>
<td>Multiple receptors</td>
<td></td>
</tr>
</tbody>
</table>

### Antiemetics by Receptor Activity

<table>
<thead>
<tr>
<th>Pure Antagonists</th>
<th>Mixed Antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Receptor</strong></td>
<td><strong>Drug</strong></td>
</tr>
<tr>
<td>( D_2 ) (central)</td>
<td>Haloperidol</td>
</tr>
<tr>
<td>- peripheral</td>
<td>Metoclopramide (Reglan)</td>
</tr>
<tr>
<td>( H_1 )</td>
<td>Diphenhydramine (Benadryl)</td>
</tr>
<tr>
<td>Ach</td>
<td>Scopolamine</td>
</tr>
<tr>
<td>- peripheral</td>
<td>Hyoscymine (Levsin)</td>
</tr>
<tr>
<td>( SHT_3 )</td>
<td>Ondansetron (Zofran)</td>
</tr>
</tbody>
</table>
Evidence supports the use of cannabinoids for CINV

- FDA approved for refractory CINV
- Superior to dopamine antagonists in preventing CINV
- +/- evidence that cannabinoids and dopamine antagonists are superior to either alone
- Side effects have lowered adoption

Statkin NE. J Support Oncol 2007 5;1-9

Acupuncture

- Systematic review of 41 RCTs
  - Some evidence for cancer-related fatigue, CINV
  - Conflicting evidence for cancer-related pain, hot flashes and hiccups
  - Insufficient evidence for xerostomia, dyspnea
  - Conclusion: need more evidence

Other options?

- Behavioral treatments
  - relaxation, imagery, music, distraction

- Ginger (*Zingiber officinale*)
  - Effective dose: 100 mg, corresponding to 2 g of rhizome BID
  - Anticholinergic and antiserotonergic
  - Prokinetic effects on gastric motility: can trial if metoclopramide side effects

Refractory Nausea and Vomiting

1. Re-evaluate for additional causes
2. Increase dose of selected agents
3. Ensure antiemetic regimen has both standing and prn agents
4. Consider adding an additional or rotating to a different drug in the same class
5. If above strategies are ineffective consider:
   - Olanzapine
   - Cannabinoid

Refractory Nausea and Vomiting

- Use antiemetic side effect profiles to your advantage, not disadvantage
  - Ondansetron: constipation
  - Haloperidol or olanzapine: antipsychotic, sedation
- Caution: try to avoid using multiple agents from same class to minimize side effects
  - Prochlorperazine + metoclopramide + haloperidol

- Ginger (*Zingiber officinale*)
  - Effective dose: 100 mg, corresponding to 2 g of rhizome BID
  - Anticholinergic and antiserotonergic
  - Prokinetic effects on gastric motility: can trial if metoclopramide side effects
Potential Side Effects of Treatment

- **Akathisia**
  - Early or late manifestation
  - Restlessness, frequent position changes

- **Tardive Dyskinesia**
  - Hyperkinetic movement disorder associated with neuroleptics
  - May become persistent even with withdrawal of drug

Malignant Bowel Obstruction (MBO)

- **Etiology:**
  - Extrinsic: tumor, radiation induce fibrosis, adhesions
  - Intraluminal: tumor in lumen or infiltration
  - Functional: tumor infiltration of mesentery or nerves

Partial vs Complete

- **Partial**
  - bowel rest
  - NG tube
  - test dose metoclopramide
  - +/- steroids
  - if refractory: octreotide

- **Complete**
  - avoid metoclopramide (and ginger?), NG tube
Management of Complete MBO

- Surgical resection
- Endoscopic stenting:
  - Best with stenoses < 4cm
  - Complications: migration, obstruction, perforation (0.5%-4%)
- Steroids:
  - Reduce inflammation → decrease stenosis, distension
  - Dexamethasone 0.25-1 mg/kg/d for < 10 days
  - NNT 6 (resolved 1/6 patients with low morbidity)


Management of Complete MBO

- Somatostatin analogues (octreotide)
  - Decreases splanchnic and portal blood flow
  - Decreases secretions
  - Increases motility and reabsorption of water
  - Start with 50-200 mcg SC q8h; if prolonged need anticipated, give LAR depot 20 mg IM
  - Overlap SC for 2 weeks with depot

Preventing MBO

Which doesn’t belong … and why?
- Psyllium
- Polyethylene glycol
- Docusate + Senna
- Bisacodyl
Preventing MBO

- Stop non-soluble fiber
- Bowel regimen
- Avoid anticholinergics
- Limit ondansetron
- Correct metabolic imbalances

...so back to Mr. B

- 49 yo M w/advanced colon cancer, progressed through chemo, waiting to enroll in a trial, admitted for N/V
- Nausea worse with movement/ingestion of big pills
- Vomiting daily after meals x1 week
- Emesis is partially digested food
- + heartburn, + odynophagia
- - fevers, headaches, focal weakness
- Denies constipation, but wife says his last BM was 1 week ago
- PMHx: DM2 (x9 years), depression, insomnia

Mr B: A partial differential

- Vestibular:
- Obstruction:
- Motility:
- Inflammation:
- Toxins/Medications:
- Intracranial:
- Nerves:
- Gums/oropharynx:
Mr B: A partial differential

- Vestibular: worse with movement
- Obstruction: constipation, peritoneal carcinomatosis, squashed stomach syndrome
  - Zofran, TCA, hypokalemia (causes ileus), diabetic (gastroparesis), dehydration
- Motility: diabetic gastroparesis, opioid induced
- Inflammation: CINV, when was last treatment, how emetogenic?
- Toxins/Medications: uremia, Fentanyl (always suspect new meds)
- Intracranial: less likely
- Nerves: associates n/v with hospital and CTX
- Gums/oropharynx: GERD, esophagitis/thrush

Initial plan for Mr. B

- Treat constipation
  - Bowel regimen
  - Replete K+
  - D/c zofran (no role from our differential, not CINV)
  - Methylnaltrexone 8mg <136 lbs, 12mg >136 lbs, 60% laxation within 4 hours, NNT 2.2
- Treat thrush/esophagitis
- Hydration for pre-renal cause of AKI and uremia

Mr. B: evaluation of treatment

- Over the next few days he has multiple large BMs
- Less vomiting & nausea overall, but still feeling nauseated after meals
- Odynophagia improving
Mr. B: Next Steps in Treatment

- Treat dysmotility
  - Metoclopramide (5-10mg IV/po TID 30 minutes prior to meals and at bedtime)
  - D/c prochlorperazine, best to avoid multiple anti-dopaminergics

A few more resources...

- http://pinkbook.dfcio.org/
The case of Ms. M

Ms. M is a 76 yo former smoker, hx COPD with newly diagnosed met NSCLC to bone, liver, adrenal glands

HPI:
- Worsening dyspnea, both exertional and at rest
- Chest tightness, increased work of breathing
- Pain in back with deep inspiration
Case of Ms. M

- Physical Exam:
  - Vital Signs: RR 22, 86% on RA, 94% on 6L
  - CV: elevated JVP, 1+ pitting edema
  - Pulm: shallow breathing, decreased BS on left, basilar crackles

Dyspnea

- How do you define dyspnea?

ATS definition of dyspnea

“...a term used to characterize a subjective experience of breathing discomfort that is comprised of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social, and environmental factors, and may induce secondary physiologic and behavioral responses.”

ATS 1999; Am J Respir Crit Care Med 159:321-340
How is Dyspnea Diagnosed?

- Gold standard: patient report
- Respiration rate, pulse oximetry, arterial blood gases are not useful guidelines
- Patients may be hypoxic, but not dyspneic; dyspneic, but not hypoxic

Respiratory Center = Medulla

- Cognitive/emotional factors
  - Central Chemoreceptors (CO2)
  - Peripheral Chemoreceptors (O2)
- Pulmonary Afferents
  - Stretch
  - Irritant
  - Alveolar C-fibers
- Other Afferents
  - Mechanoreceptors
  - Diaphragm
  - Intercostals
  - Accessory Muscles

Management of Dyspnea

- Most importantly, the underlying cause should be identified and treated, if possible.
Additional Strategies

- Interventional Procedures
- Non-pharmacologic Measures
- Pharmacologic Measures

Interventional Procedures

- Pleural effusion - thoracentesis, pleural catheter
- Ascites - paracentesis
- Pericardial effusion - pericardiocentesis, pericardial window
- Obstructive mass - large airway stenting
- SVC syndrome: intravascular stenting

Nonpharmacologic Strategies

- Nursing-led rehabilitation programs
- Cognitive and behavioral interventions
  - Breathing techniques
  - Relaxation techniques
  - Coping with psychological challenges of dyspnea
- Several trials in cancer patients: improved dyspnea and quality of life

Ben-Aharon et al. 2008, J Clin Onc, 26:2396-2404
Breathing techniques can be taught

Stimulation of V2 distribution

Oxygen Therapy: Mixed Results

- Hypoxemic:
  - Terminally ill cancer patients: Some studies show significant symptom relief, others show no difference between air vs oxygen
  - Severe COPD: long-term oxygen therapy → improved QoL and survival
  - Non-hypoxemic: no difference in air vs. oxygen

Oxygen Therapy: Conclusion

- Hypoxemic: consider trial oxygen
- Non-hypoxemic: oxygen not necessary

Pharmacologic Measures

- Opioids
- Benzodiazepines

Pharmacologic Measures: Opioids

- First-line therapy for symptomatic control of dyspnea
- Mechanism of action is not fully understood
  - Cardiovascular effect: vasodilation
  - Reduce medullary sensitivity to hypercarbia
  - Opioid receptors in tracheobronchial tree
  - Anxiolytic effect
Opioids for Dyspnea

- Meta-analysis: cancer, COPD, CHF, ILD
  - Significant relief of dyspnea
  - No deaths attributable to opioids

- Palliative care unit patients
  - Significant relief of dyspnea
  - No respiratory depression
  - CO2 and O2 levels stable

Clemens KE. J Pain Symptom Manage 2007; Clemens KE. Support Care Cancer 2008

Opioids for Dyspnea

- Cochrane review of opioids in advanced disease and terminal illness
  - 26 studies
  - Some evidence for opioids as beneficial
  - No evidence for nebulized opioids

Cochrane Database, March 2016

Opioid Dosing

- Doses needed to relieve dyspnea are often less than those needed for relief of pain

- Opioid naïve patient
  - Morphine 5 mg PO q4h
  - Oxycodone 2.5-5 mg PO q4h
  - Hydromorphone 1 mg PO q4h

- Chronic opioids: increase by 25-50% to treat dyspnea

Thomas JR and von Gunten CF 2002; Lancet Oncol 3: 223-28
Opioid Dosing

- For breakthrough, give an equivalent dose every 1-2 hr prn
- Titrate in increments of 50-100% q24hrs
- Once 24-hour opioid requirement in determined, can consider long-acting

Thomas JR and von Gunten CT 2002; Lancet Oncol 3: 223-28

Pharmacologic Measures: Anxiolytics

DYSPEA  ANXIETY

Benzodiazepines

- Data insufficient to recommend its use alone
- Some studies support its use as adjunct to opioids
- Possible regimens (scheduled or prn):
  - Lorazepam 0.5-1 mg po/IV q4h prn
  - Diazepam 2.5-5 mg po q6-8h prn
  - Clonazepam 0.25-1 mg po q12h
  - Midazolam 0.5 mg IV (severe symptoms/emergency)

Abrahm, JL. A Physician’s Guide to Pain and Symptom Management in Cancer Patients 2014
Other Pharmacologic Measures

- Glucocorticoids
  - Bronchospasm
  - Lymphangitic spread
  - Radiation pneumonitis
- Bronchodilators:
  - Bronchospasm and cough
- Anti-cholinergics
  - Copious secretions

Case of Ms. M

- Ms. M is a 76 yo former smoker, hx COPD with newly diagnosed met NSCLC to bone, liver, adrenal glands
- HPI:
  - Worsening dyspnea, both exertional and at rest
  - Chest tightness, increased work of breathing
  - Pain in back with deep inspiration

Case of Ms. M

- Physical Exam:
  - Vital Signs: RR 22, 86% on RA, 94% on 6L
  - CV: elevated JVP, 1+ pitting edema
  - Pulm: shallow breathing, decreased BS on left, basilar crackles
Case of Ms. M

- What is your differential diagnosis?

Differential Diagnosis

- Pulmonary edema
- Pleural effusion
- Pulmonary embolism
- Disease progression: lymphangitic spread or airway obstruction
- COPD exacerbation
- Cardiac ischemia
- Restriction due to pain

Studies: Chest X-ray

- Bilateral pleural effusions L > R
- Mediastinal mass
Studies: Chest CT

- No PE
- Extensive septal thickening: lymphangitic carcinomatosis
- 4.7 x 2.9 cm subcarinal soft tissue mass → mass effect, narrowing of the left main bronchus
- Large left pleural effusion; moderate right pleural effusion
- Ground glass opacities
- Emphysematous changes
- Compression fracture of T7, metastases

Interventional Treatment Options

- Pleural effusion
  - Thoracentesis
  - Chest tube, PleurX catheter
  - Pleurodesis
- Large airway obstruction
  - Palliative stent
- T7 compression fracture
  - Radiation therapy?
  - Kyphoplasty?

Pharmacologic Treatment

- Opioids: symptom relief
- Bronchodilators: COPD, small airway obstruction
- Diuretics: pulmonary edema, pleural effusion
- Steroids: lymphangitic spread
Nonpharmacologic Strategies

- Oxygen (in setting of hypoxia)
- Bedside fan
- Cool cloth
- Breathing techniques

Case of Ms. M

Following a successful stay in rehab, Ms. M returns to clinic. Her dyspnea has improved. However, she reports significant fatigue.

Cancer Related Fatigue

- “distressing, persistent subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to activity and that interferes with usual functioning”
- Not relieved by rest

NCCN Guidelines Cancer-Related Fatigue, Version 1.2013
Cancer Related Fatigue

- Prevalence in cancer patients: 48-75%
- Fatigue is common and often undertreated
- Profound effect on quality of life

Etiologies

- Direct effect from cancer
- Cancer treatment
  - Medication
  - Radiation therapy
- Medical illness and complications
  - Anemia
  - Hypoxemia
  - Renal and other organ dysfunction
  - Electrolyte abnormalities
  - Dehydration
  - Hormone imbalance (hypogonadism, hypothyroidism)
  - Infection
  - Malnutrition
  - Physical symptoms (nausea, pain, dyspnea, etc)

Etiologies

- Deconditioning
- Mental health
  - Depression
  - Anxiety
  - Insomnia
Management Strategy

- Treat underlying disease
- Correct reversible causes
- Control physical symptoms

Non-pharmacologic
- Exercise
- Optimize sleep
- Cognitive behavioral strategies
- Acupuncture

Pharmacologic
- Glucocorticoids
- Psychostimulants

*within goals of care

Exercise

- Cochrane review of 56 RCTs concluded that exercise was effective for cancer related fatigue
- Aerobic exercise and strength training can increase functional capacity, reduce fatigue and muscle wasting

Optimize Sleep

- Stress reduction and cognitive behavioral therapy are effective in managing insomnia in cancer patients
- Sleep hygiene
  - Consistent schedule
  - Limit naps
  - Avoid caffeine late in day
  - Regular exercise


Cognitive Behavioral Interventions

- Multiple small RCTs and one meta-analysis support the use of behavioral and psychosocial interventions during cancer therapy
- Behavioral strategies to manage fatigue
- Prioritizing and pacing activities
- Self-monitoring with log or diary


Acupuncture

- Acupuncture is potentially beneficial in reducing fatigue
- Several randomized trials
- Limitation: control group = no treatment, rather than sham acupuncture control


Glucocorticoids

- RCT of 84 patients with cancer related fatigue
  - Dexamethasone 8 mg daily vs. placebo x 14 days → improved fatigue and quality of life indices
- Consider glucocorticoids in terminal phase
- Side effects limit long-term use

J Clin Oncol 2013 Sept; 31(25):1076
**Psychostimulants**

- Data is variable
- Consider trial if nonpharmacologic strategies are insufficient:
  - Methylphenidate 5 mg qam and noon (max 40 daily)
  - Modafinil 100-200 mg qam and noon (max 400 daily)
- May be helpful in opioid-related sedation

**Other medications**

- Antidepressants – fatigue and depression
- Testosterone – fatigue and hypogonadism

**Questions or comments?**