Dying without Dyspnea

Dyspnea

• 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 physiological and behavioral responses.
  – Consensus statement of the American Thoracic Society, 1999

• ...uncomfortable awareness or sensation of breathing
  – Air Hunger
  – Suffocation
  – Choking
  – Heavy breathing
  – Chest Tightness
  – Rapid Shallow Breathing
  – Del Fabbro Pall Med 2006;9:422-436
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**Respiratory Drive**

- Low PO$_2$
- High PCO$_2$
- pH

- Peripheral + Central Chemoreceptors
- Respiratory Center
- Cerebral Cortex
- ↑Respiratory Rate + Effort

**Mechanoreceptors**

- Upper-airway and facial receptors
  - May modify the sensation of dyspnea
  - Cold air, fan, open window
  - Trigeminal nerve distribution
- Lung receptors
  - Stretch receptors in the airways (terminate respiration)
  - Irritant receptors (mechanical or chemical irritant)
  - J receptors (alveolar interstitial congestion)
- Chest wall receptors

**Symptoms of Dyspnea**

- In hospice and palliative care, patients’ caregivers overrate symptom scores of dyspnea, pain and constipation

- Physicians:
  - consistently underrate symptoms of dyspnea
  - optimistically prognosticate life expectancy
Reporting Dyspnea

• “An inability to report symptom distress is not synonymous with an inability to experience suffering.”

– Patients Who Are Near Death Are Frequently Unable To Self-Report Dyspnea
  • Journal of Palliative Medicine, 2009
  • Campbell, Templin, Walch

Dyspnea in Dying NH Patients

• Study revealed 62% of NH patients have dyspnea 48 hours prior to death
• Dyspnea most prevalent symptom prior to death
• 51% are cognitively impaired
• Dyspnea not treated in 23%

– Teno JM JAMA 2004;291:88-93

Dyspnea

• Subjective symptom
• Objective findings (tachypnea, oxygen saturation) may not adequately reflect the severity of dyspnea

• Treatment management should be focused on the symptoms, not the objective findings...spirometry, RR, oxygen saturation
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Dyspnea

- Dyspnea does not always correlate with the degree of hypoxemia
  - 100 patients with advanced cancer with dyspnea, only 40% were hypoxic
  - Air vs. oxygen studies not conclusive that oxygen is better

Visual Analog Scale (VAS)

<table>
<thead>
<tr>
<th>SEVERITY</th>
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<tr>
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<td>6</td>
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<td>7</td>
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<td>10</td>
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Modified Borg Scale
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Dyspnea in Terminal Illness
- Lung cancer
- All cancer
- COPD
- CHF
- Pleural effusion
- Pneumonia
- Pulmonary embolism
- Anemia
- Ascites
- SVC Syndrome
- Pneumothorax
- Radiation Pneumonitis

Dyspnea Relief in Advanced Cancer
- Interventions for Alleviating Cancer-Related Dyspnea: A Systematic Review
  - Ben-Aharon, Gafter-Gvili, Leibovici, and Stemmer
  - J Clin Oncol 26:2396-2404
  - Systematic review of randomized controlled trials assessing all pharmacologic and non-pharmacologic interventions for palliation in cancer patients...
  - 18 trials; 14 pharmacologic
    - 7 opioids (256 pts), 5 oxygen, 1 helium enriched air, 1 furosemide
    - 4 non-pharmacologic

- Dyspnea in Advanced Cancer
  - Incidence up to 90% prior to death, 60% at presentation
  - Even low intensity dyspnea compromises function
  - Benefits of oxygen are not well established
  - Opioids are included in the first line therapy
  - Continuous and breakthrough dyspnea
    - Breakthrough 5-6 times a day as short as 5 min
    - Short acting opioids onset longer than 5 min
    - Suggests consideration for long acting opioids
Opioids

• COPD and interstitial lung disease
  – Most studies conclude opioids relieve dyspnea and are beneficial in improving symptoms

• Advanced Cancer
  – All studies prove benefit

Opioids

• Mechanism of relieving dyspnea is unknown
  – Depression of opioid receptors in the lung, spinal cord and CNS
  – May diminish ventilatory response to hypoxemia and hypercapnia
  – Reduce anxiety and subjective sensation of dyspnea
  – Venodilatation of pulmonary vessels (reduce preload to heart)

Cancer, Dyspnea and Opioids

• Respiratory depression a feared side effect of opioids
• No higher risk for respiratory depression and no differences in pCO2-levels in opioid naive patients than in opioid tolerant patients.
• First opioid dose resulted in decrease in dyspnea and RR
  – Clemens Pall Med 2008;11:204-216
Last Week of Life

- Retrospective study 238 pts in ICU who died
- Concluded the appropriate use of opioids does not shorten life

— Thorns Lancet 2000;3556:398-399

Opioid Administration

Terminal Ill Cancer

- Opioids better at relieving dyspnea than placebo
- Inhaled/nebulized morphine trended toward improvement over placebo, not statistically better
- Nebulized morphine vs systemic morphine no difference in dyspnea relief
  — Not recommended, low bioavailability
- Systemic, subcutaneous significantly more effective than placebo
- Morphine did not increase somnolence

Advanced Cancer Patients

- Morphine plus midazolam better than either morphine or midazolam alone rescue

— Navigante J Pain Symptom Manage 31:38-47
Benzodiazepines in Terminally Ill Cancer Patients with Dyspnea
- No evidence to support routine use of benzodiazepines for dyspnea
- Addition of benzodiazepines likely enhances the effect of the opioids
- Anxiety, fear, panic, sensation of impending death
- Benzodiazepines widely used without evidence of benefit

Dyspnea and Benzodiazepines
- Benzodiazepines
  - Effective in palliating anxiety in terminally ill patients, more so in patients with life expectancy of days to weeks
  - Sedating, habit forming, increase depression, increase risk of falls, short term memory loss
  - Maintenance: low dose long-acting benzodiazepine (diazepam 0.5 mg - 1 mg q 12 hrs) and short-acting lorazepam for breakthrough

Anxiety and Dyspnea
- Anxiety
- Dyspnea
  - Suffocation
  - Impending Doom
  - Fear of Death
- Hours, days, weeks vs chronic use
Oxygen and Advanced Cancer

- Oxygen not superior to air
  - Except in hypoxic cancer patients
  - Non-hypoxic: no difference in dyspnea or 6 min walk test
- May give benefit even with normal oxygen saturation
- Stimulate trigeminal nerve endings (fan)
- Potent placebo effect
- Few side effects
- Expensive and burdensome

Oxygen vs. Air

- Randomized, double blind, cross over, 51 patients, average age 65, over half lung cancer, very short term study
- Hypoxic and normoxic patients with advanced cancer
- No significant difference between oxygen and air
- Subgroup of hypoxic patients also did not show difference and no correlation with degree of oxygenation
  - Phillip J Pain Symptom Manage 2006;32:541-550

Nebulized Furosemide and Cancer Patients with Dyspnea

- Nebulized furosemide showed a trend toward worsening of dyspnea when compared to placebo
Cancer and Dyspnea

**Steroids**
- Cancer
  - Carcinomatous Lymphangitic spread
- Superior Vena Cava Syndrome
  - Tumor compression

**Bronchodilators**
- Lung cancer

Non-pharmacologic Treatment of Dyspnea in Terminally Ill Cancer

- Nursing led interventions were beneficial
  - Counseling
  - Relaxation
  - Coping strategy
- Acupuncture was not beneficial
  - Farrell PC-FACS Issue 43- June 16, 2008 Pall Med
  - Ben-Aharon L Clin Oncol 2008;26:2396-2404
  - Interventions for relieving cancer-related dyspnea: A systematic review

Studies to Relieve Dyspnea Terminally Ill Cancer

- Few studies
- Small numbers of patients
- Short follow up periods
- No systematic evaluation
- No consensus statements or guidelines
Dyspnea in Non-Cancer Patients

- Manage the underlying illness
  - Cardiac, pulmonary
  - Look for secondary causes (pneumonia, effusion)
- Manage dyspnea symptomatically
  - Opioids, non-pharmacologic (fans)
  - Psych-social support

COPD

- COPD affects 14-20 million Americans
- Fourth leading cause of death; 110,000 / year in USA
- Symptoms in late stages often worse than patients with advanced lung cancer
- Bronchodilators and steroids do not change the natural course or the mortality of COPD.
- There is evidence of modest reduction of exacerbations with bronchodilators and steroids
- 50% of patients discharged from hospital for exacerbation are readmitted within 6 months
  - Snow 2001;134:595-599

COPD and Opioids

- Consider opioids for advanced COPD patients, not just those imminently dying
- Immediate release and sustained release opioids are beneficial
- Reduce the sensation of dyspnea
- Oral and parenteral are effective, nebulized opioids are ineffective
- Lack of adverse effect on blood gases
  - Rocker Pall Med 2007;10:783-797
COPD and Depression

- Palliating anxiety and depression in patients with chronic dyspnea
  - Anti-depressants
    - SSRIs and Tricyclics
    - SSRIs reduce panic disorder in COPD patients
    - Buspirone, reboxetine, venlafaxine effective
    - Positive effects in 2 weeks, full effect in 3-4 weeks

COPD and Oxygen

- Long term oxygen therapy improves:
  - Survival
  - Pulmonary hemodynamics
  - Exercise capacity
  - Neuropsychological function
  - Decreased sensation of dyspnea
- Potential for toxicity in COPD
  - Hypercarbia and respiratory failure

CHF

- Reassess and optimize medications
- Assess for reversible causes
  - Pleural effusion
  - Pericardial effusion
- Dysrhythmias
- Other disease, e.g. COPD
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CHF

• Diuretic therapy
  – IV or SQ route
  – Continuous infusion
    • 3-200 mg/hr (10-20 mg/hr in most patients)
    • ACC/AHA 2009 guidelines for heart failure: 40 mg IV load followed by 10-40 mg/hour infusion
  – Loop resistant (furosemide)
    • Add thiazide: HCTZ (25-100 mg/d) or metolazone (5-20 mg/d)
• Watch electrolytes if death is not imminent

CHF

• IV Inotrope Therapy
  – Dobutamine, milrinone, dopamine
  – Primarily used in hospitalized patients
  – Can provide a bridge to allow patients to discharge home to die
  – Intermittent infusions of questionable benefit

Terminal Secretions

• Death rattle
• As often as 90% in dying patients
• Lose ability to swallow, cough, clear secretions
• Disturbing to family and staff
• Does not cause suffering
  – Upper secretions
  – Lower secretions
• Reposition, medications, rarely suction
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### Pharmacologic Methods of Secretion Reduction

<table>
<thead>
<tr>
<th>Generic Drug</th>
<th>Trade Name</th>
<th>Administered</th>
<th>Starting Dose</th>
<th>Onset</th>
<th>Estimated Daily Price at Maximum Use</th>
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<tr>
<td>hyoscine hydrobromide (scopolamine)</td>
<td>Transderm Scop</td>
<td>patch</td>
<td>1 mg/3 days</td>
<td>12 hrs</td>
<td>$3.00/day</td>
</tr>
<tr>
<td>hyoscine hydrobromide (scopolamine)</td>
<td>Transderm Scop</td>
<td>patch</td>
<td>1 mg/3 days</td>
<td>12 hrs</td>
<td>$3.00/day</td>
</tr>
<tr>
<td>hyoscine hydrobromide (scopolamine)</td>
<td>Serax</td>
<td>0.2 mg</td>
<td>rapid</td>
<td>0.2 mg SC q 4 hrs</td>
<td>$10.00/day or cont. infusion 0.2 mg/hour</td>
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<tr>
<td>glycopyrolate</td>
<td>Robinul</td>
<td>injection (SC, IV)</td>
<td>0.2 mg</td>
<td>1 min</td>
<td>0.2 mg SQ q 2 hrs</td>
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<tr>
<td>glycopyrolate</td>
<td>Robinul</td>
<td>injection (SC, IV)</td>
<td>0.2 mg</td>
<td>1 min</td>
<td>0.2 mg SQ q 2 hrs</td>
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<tr>
<td>atropine</td>
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<td>0.4 mg q 5 doses</td>
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<td>1 gtt (1%)</td>
<td>30 min</td>
<td>4 gtt x 6 doses</td>
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### Cheyne Stokes Breathing

- CSB is characterized by cyclic crescendo-decrescendo respiratory effort and airflow during wakefulness or sleep, without upper airway obstruction.
- Cheyne-Stokes respiration is characterized by recurrent central apnea alternating with a crescendo-decrescendo pattern of tidal volume. It is the most commonly recognized abnormal respiratory pattern after stroke, but in approximately 90 percent of patients it reflects underlying cardiopulmonary disease.
- Initially believed to be due to bilateral forebrain disease or diffuse bihemispheric disease, Cheyne-Stokes respiration is now known to occur with unilateral hemispheric and brainstem infarcts.
- Cheyne-Stokes respiration has little prognostic value.
- However, hypocapnia is almost always present and may require treatment to prevent cerebral vasoconstriction and exacerbation of the underlying neurologic condition.
- Hypoxemia is frequently present due to concomitant heart and lung disease.
Abnormal Respirations

- Periodic breathing — Periodic breathing, a variant of Cheyne-Stokes respiration, is characterized by regular, recurrent cycles of changing tidal volumes in which the lowest tidal volume is less than half the maximal tidal volume in that cycle.
- It is the most frequent abnormal respiratory pattern directly related to stroke rather than underlying systemic disease, occurring in approximately 25 percent of patients. Periodic breathing may be more common among patients with subarachnoid hemorrhage.

Ataxic Breathing

- Ataxic breathing — Ataxic breathing is a rare respiratory pattern characterized by an erratic rate and depth of breathing, alternating with interspersed episodes of apnea.
- It is the only respiratory pattern with true localizing value and is indicative of a medullary lesion.
- It may occur in patients with neurodegenerative disorders (such as Shy-Drager syndrome) but when developing acutely should always raise suspicion for a medullary stroke.

Gaspering, Agonal, Guppy Breathing

- Gasing — Gasing is an abnormal breathing pattern characterized by an attenuated inspiratory period followed by a disproportionately long period of expiration.
- Associated abnormal involuntary movements such as platysma contraction and neck hyperextension are common.
- Gasing is more commonly seen in medullary strokes but overall has poor localizing value. Respiratory failure almost invariably ensues.
**Opioid Dosing Considerations**

- **Opioid Naïve**
  - Morphine
  - **Oral**
    - Low dose: 2.5 mg q 4 hours po
    - High dose: 5 mg q 1 hour po
  - **SC**
    - 2 mg q 10-20 minutes pm
  - Titrate to effectiveness
- **Opioid Tolerant**
  - 25% increase and titrate
- Respiratory depression does not occur with prudent dosing

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**Dyspnea Acute Management COPD**

- **Bronchodilators**
  - Short acting bronchodilators:
    - beta-agonists
    - ipratropium
- **Steroids**
  - High dose, tapering
- **Antibiotics**
  - Data does not support novel, high cost antibiotics
- **Opioids**
  - Naïve vs. tolerant
  - SQ v oral
- **Benzodiazepines**
  - Monitor closely, not universally recommended

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**Dyspnea Acute Management CHF**

- **Diuretics**
  - Oral v IV infusion
- **Opioids**
- **Benzodiazepines**
  - Caution
- **Inotropics**
**Dyspnea**

**Acute Management Cancer**

- Opioids
- Bronchodilators
- Steroids
- Antibiotics
- Benzodiazepines
  - Determine goals of care
  - Estimate life expectancy

**Dyspnea and Survival**

- Does not appear to be an independent marker for limited life expectancy
- Combination of delirium, anorexia and dyspnea do have predictive value in terminally ill patients for shorter survival in general disease and advanced cancer

  - Pall Med 2007;10:904-909

**Palliative Sedation**

- Use of (proportional) sedation to manage refractory symptoms in dying patients is a therapeutic option
- Intent to deliberately induce and maintain sleep but not to deliberately cause death
- Delirium most common condition
- Define refractory symptoms: difficult, challenging or really refractory
- Apply to specific individual patients
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