

Managing Dyspnea in Palliative Care



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- Medical Consultant with *Canadian Virtual Hospice*
- Pictures may be subject to copyright
- Off-label pharmaceutical suggestions will be identified

Objectives

At the conclusion of this session, participants will:

- Identify the importance of dyspnea in the context of advancing disease
- Recognize the broad differential diagnosis of dyspnea and determine when to address specific causes and when to address the symptom directly
- Describe when and how to manage pleural effusions *
- Understand the roles of oxygen and medications such as opioids and feel comfortable using them to treat dyspnea in the various points of the palliative care trajectory

Dyspnea

“one of the most distressing symptoms”

Combination of:

- **“SENSATION”** (neural activation resulting from stimulation of a receptor)
- **“PERCEPTION”** (reaction of the individual to that sensation).

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 physiological and behavioral responses*

American Thoracic Society

Causes of Dyspnea

- Pulmonary causes
 - Airway obstruction, pleural effusion, COPD, lymphangitic carcinomatosis, pneumonia, pulmonary embolism, etc.
- Cardiac causes - CHF, pericardial effusion
- Systemic causes - Anemia
- Muscle weakness - ALS, cachexia
- Intra-abdominal factors - Ascites
- Psychological

Mr. T

- 71 year old man with advanced rectal cancer, metastatic to lungs
- P.H. of CAD, a MI 6 years ago, and CHF
- In clinic for follow up, he states that he is having more difficulty walking to the mailbox, just two houses away, and he needs to rest halfway up the stairs from his basement
- He is wondering about getting some Home O2

Mrs. G

- 54 year old woman with advanced ovarian cancer, progressive despite two lines of chemotherapy, presents with increasing dyspnea
- Found to be BRCA2 POS
- Past History:
 - Mild exercise-induced asthma
 - G3P3, children ages 19,20,22
- Hemoglobin 98; Creatinine 140, eGFR 35
- Mild-moderate right pleural effusion

Mr. M

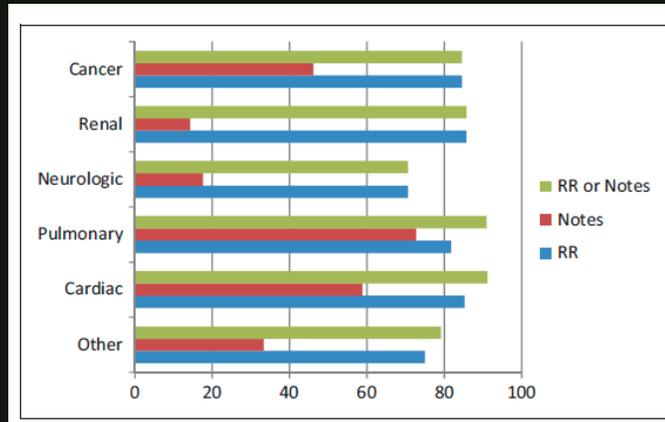
- 69 year old man with Advanced COPD
- 3 hospitalizations in the past 6 months;
 2 for COPD exacerbations, 1 for pneumonia
- Persistently dyspneic
- Admitted to hospital
- A locum physician has suggested morphine, but the nurse comes to you, asking you whether that is consider safe care

Assessment of Dyspnea

- Pattern
 - Intermittent
 - Continuous
 - Acute intense episodes
- Triggers
- Associated emotions
- Use scales to measure and monitor
- Investigations as needed

Dyspnea - Unrecognized and Untreated

- Retrospective review of 106 consecutive deaths in a single facility
- 89% were on Oxygen
- 46% documented to be dyspneic
- 83% tachypneic in last 24 hours of life



Morris D, Galicia-Castillo M. Dying With Dyspnea in the Hospital. *Am J Hosp Pall Med* 2017, Vol. 34(2) 132-134

Breathlessness in the Last Week of Life

- 12,778 patients from 87 palliative care services across Australia
- Breathlessness may worsen in the last months of life, but the mean severity remained stable in the final week of life.
- One in three individuals receiving specialized palliative care experienced significant breathlessness, especially in respiratory disease.

Dyspnea in the Last Days of Life

Table 5 Causes of hospital admission

Reasons for hospital admission	No of patients (%)
Delirium	3 (2.2 %)
Family fatigue	23 (16.8 %)
Gastrointestinal symptoms	16 (11.7 %)
Dyspnea	32 (23.4 %)
Hemorrhage	5 (3.6 %)
Pain	3 (2.2 %)
Fever	9 (6.6 %)
Neurological symptoms	24 (17.5 %)
Renal failure	7 (5.1 %)
Others	15 (11 %)

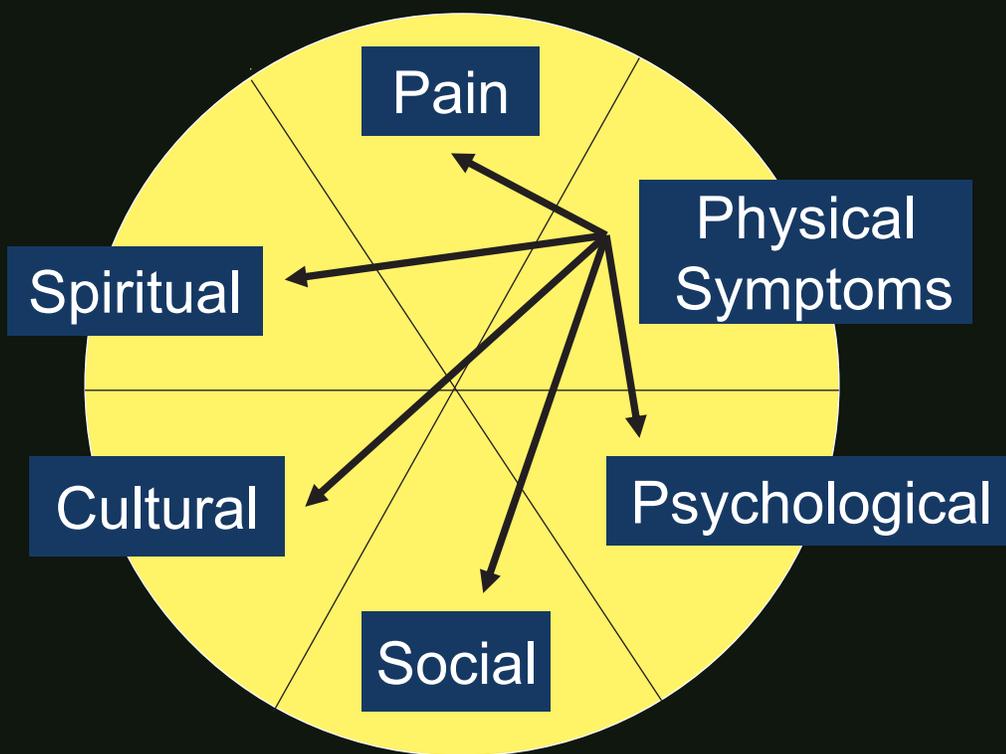
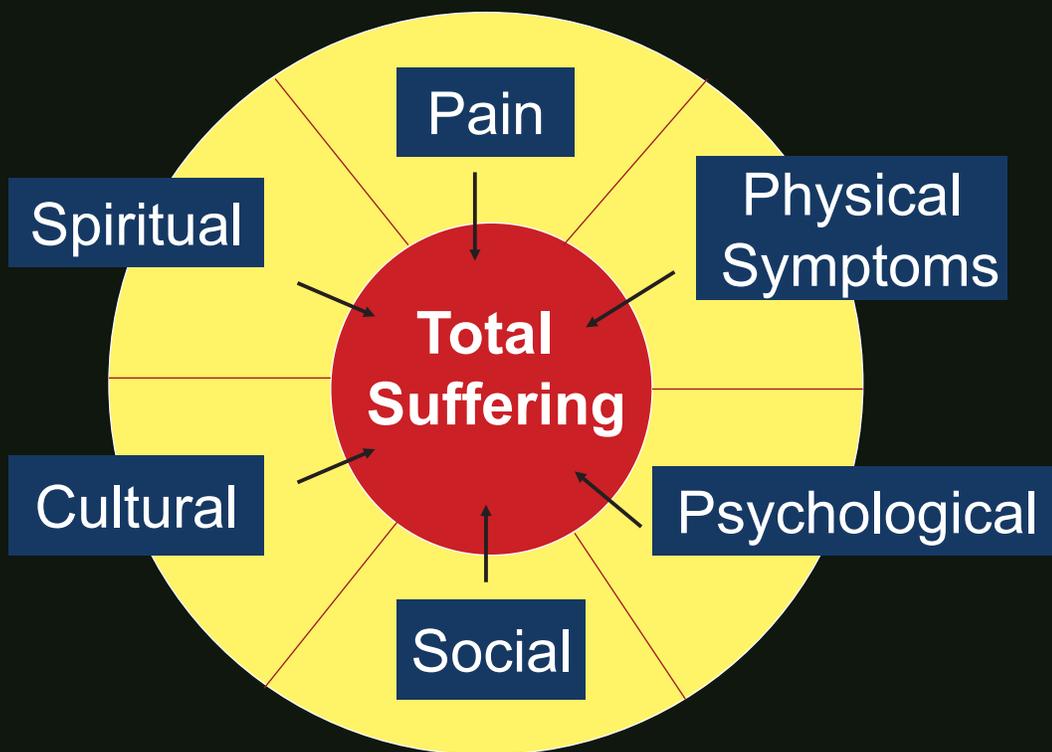
Mercadante S, et.al. The characteristics of advanced cancer patients followed at home, but admitted to the hospital for the last days of life. Intern Emerg Med (2016) 11:713–718.

Episodic Breathlessness in Advanced Cancer Patients

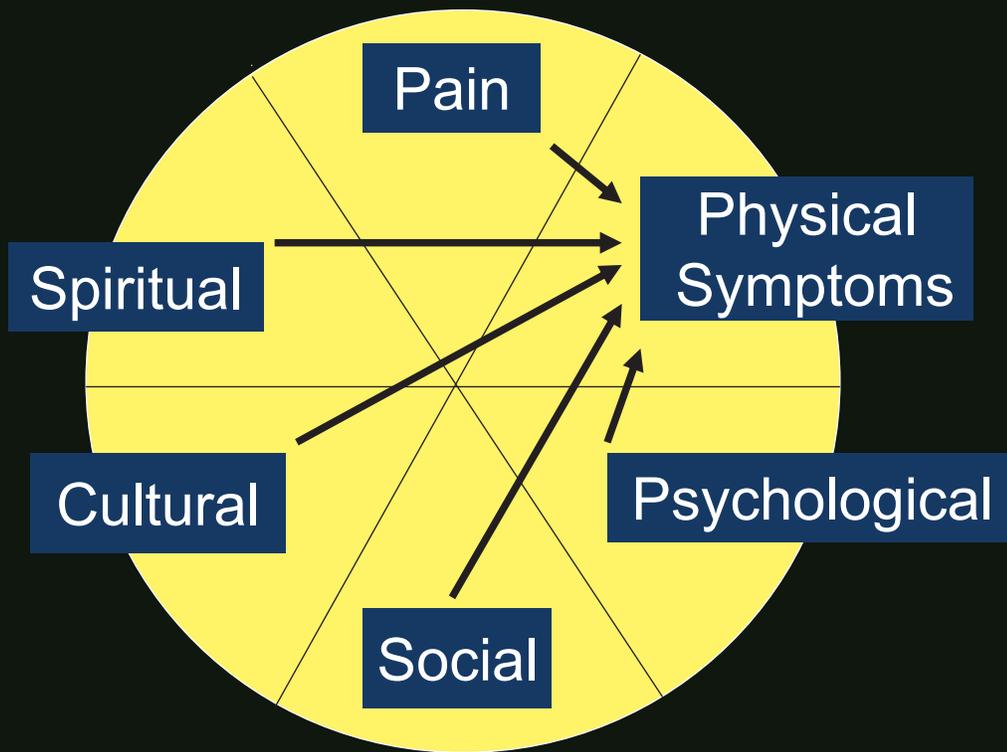
- prevalence of background breathlessness was 35.3% (122/347) – mean intensity 3.8
- prevalence of episodic breathlessness in patients with continuous breathlessness was 79.5% - mean intensity 7.1
- Frequent in advanced home cancer patients
- Severe in intensity
- Mostly triggered by activity
- Short in duration requiring rapid measures

Mercadante S, et.al. Background and episodic breathlessness in advanced cancer patients followed at home. Curr Med Res Opin, 2017(33);1: 155–160.

Total Suffering (Woodruff)

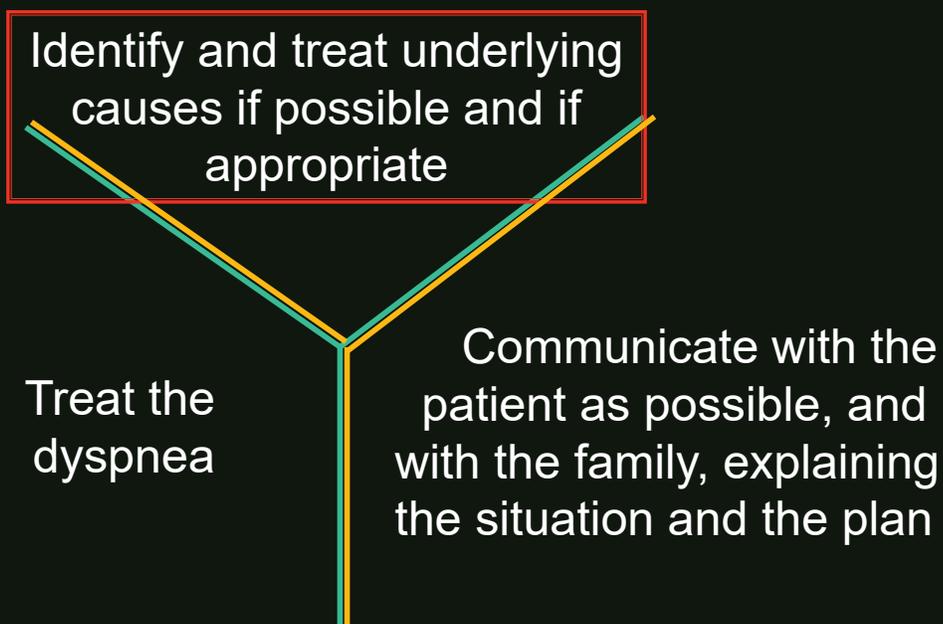


Unrelieved symptoms may cause or aggravate problems related to any of the other causes of suffering.



Unresolved suffering related to any of the other causes of suffering may cause or aggravate physical symptoms

Management Approach to Dyspnea



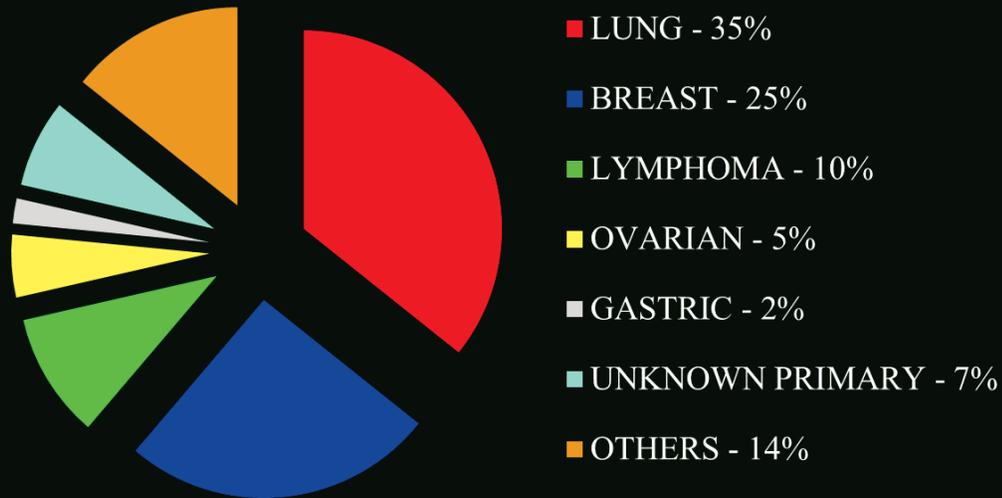
Managing Underlying Causes - Examples

- Pleural effusion – thoracentesis
- Large airway obstruction – stenting, radiotherapy
- Pneumonia – antibiotics
- Anemia – therapeutic trial of transfusion
- CHF and COPD – optimize medications
- ALS - non-invasive ventilation

Malignant Pleural Effusion

- 150,000 cases per year in USA
- Median Survival reported at 4-9 months
- Histology most often adenocarcinoma
- In patients with a known malignancy and a MPE, no malignancy is found in the fluid or pleural surface in up to 50%
- Exact mechanism is not entirely understood
- 60% of patients with pleural metastases develop MPE

Malignant Pleural Effusion Etiology



Malignant Pleural Effusion Clinical Manifestations

- Cough
- Pains – pleuritic, pressure and heaviness
- Progressive dyspnea on exertion

- Severity of symptoms often depend more on the rate of fluid accumulation than on the total amount of accumulated fluid

Ms. B

- 68 year old female with known NSCLC.
- She has been on Crizotinib for 2 months
- Presents with recent increased cough, more dyspnea on exertion, and fatigue.
- She has poor air entry in her right lower lung, and is sent for a CXR.

Ms. B

Should this effusion be drained?



Ms. B



TODAY



6 WEEKS AGO

Malignant Pleural Effusion Therapeutic options

Does every malignant effusion
require treatment?

Ms. B



TODAY



6 WEEKS AGO

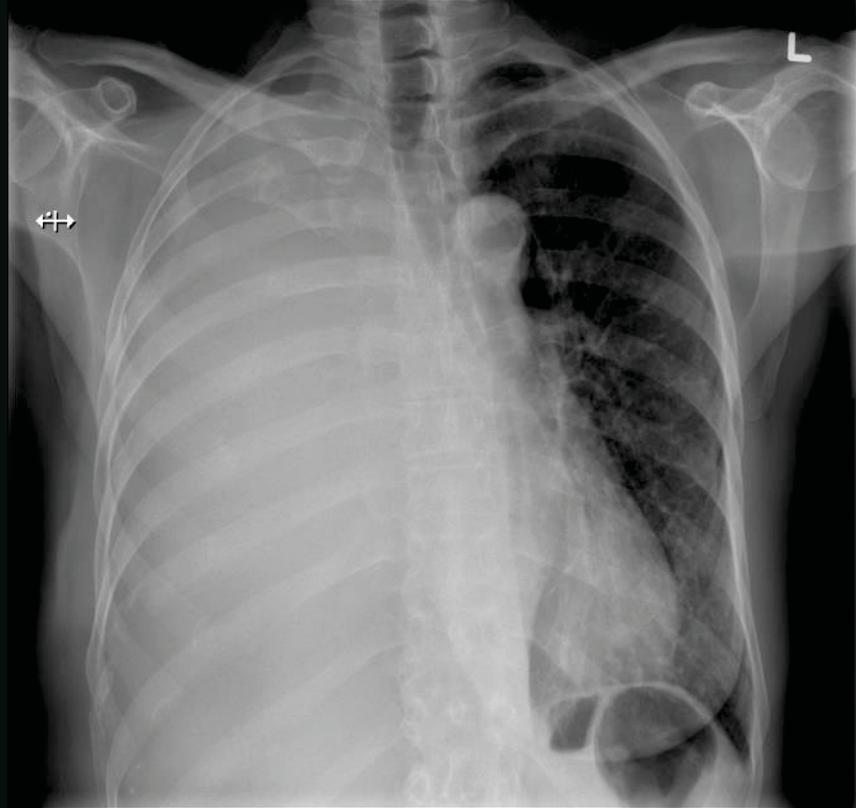


3 MONTHS AGO

Malignant Pleural Effusion Therapeutic options

- Depend on:
 - Etiology
 - Pulmonary expansion
 - Performance status
 - Symptoms
 - Estimated length of survival
- Systemic treatment vs systemic or local palliation of symptoms

Should this effusion be drained?



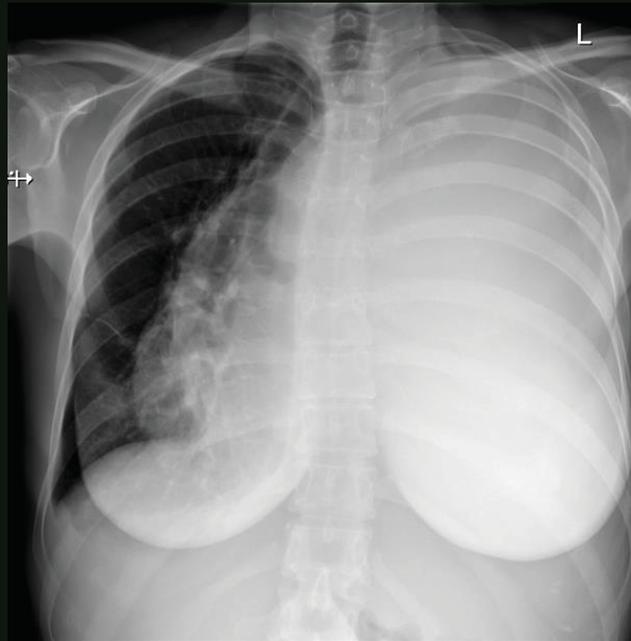
Thoracentesis - Risks

- Pain
- Bleeding / Bruising
- Infection
- Pneumothorax
- Liver injuries
- Spleen injuries
- Cardiac injuries
- Re-expansion Pulmonary Edema

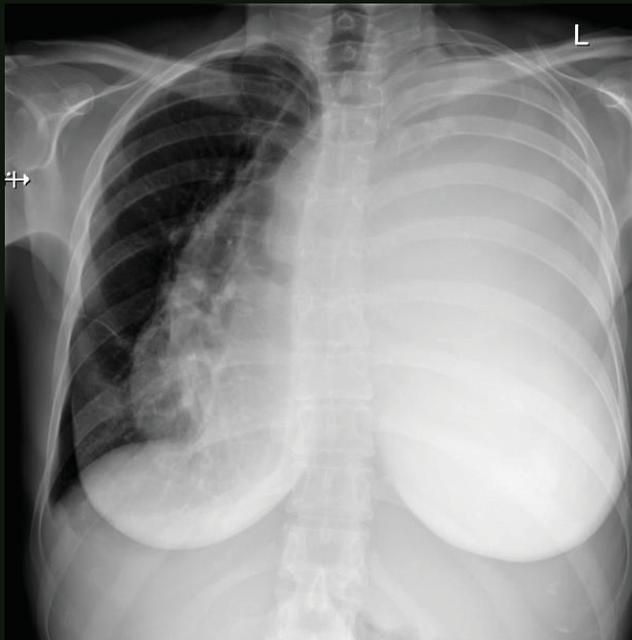


We report here a case of sonography-guided, largebore needle thoracentesis with a fatal complication due to cardiocentesis in a woman with a dilated left ventricle

Large Pleural Effusions



How much fluid can I drain with a thoracentesis?

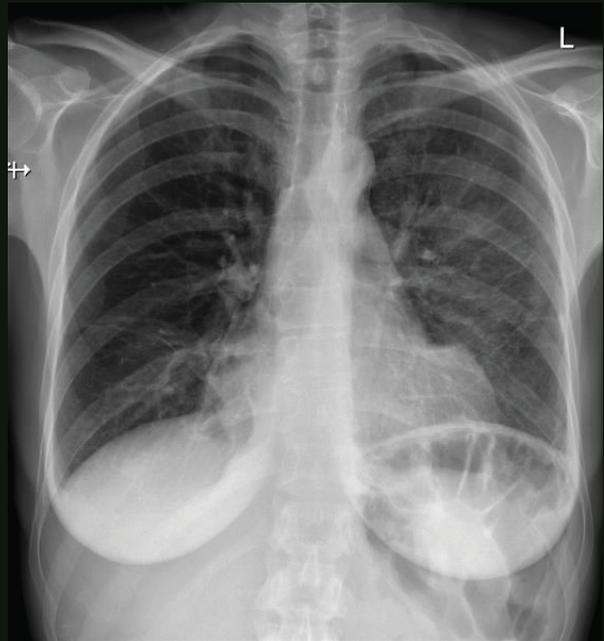


- 1) 500 mls
- 2) 1000 mls
- 3) 1500 mls
- 4) 2000 mls
- 5) 3000 mls

Large Volume Thoracentesis



BEFORE



AFTER

Large-Volume Thoracentesis and the Risk of Reexpansion Pulmonary Edema

- Prospective study of 185 patients undergoing thoracentesis of > 1 litre
- The recommendation to terminate thoracentesis after removing 1 L of fluid needs to be reconsidered

Large-Volume Thoracentesis and the Risk of Reexpansion Pulmonary Edema

- 185 Patients:
 - 98 (53%) 1-1.5 L
 - 40 (22%) 1.5-2 L
 - 38 (20%) 2-3 L
 - 9 (5%) > 3 L
- 5 patients had RPE, 4 diagnosed only on post-procedure CXR (no symptoms)
- Patients with RPE had significantly higher volumes removed than did patients without RPE
(medians, respectively: 2,400 cc and 1,420 cc)
- incidence of RPE not associated with the absolute change in pleural pressure, pleural elastance, or symptoms during the procedure

Feller-Kopman D, et.al. Ann Thorac Surg 2007;84:1656-62.

Large-Volume Thoracentesis and the Risk of Reexpansion Pulmonary Edema

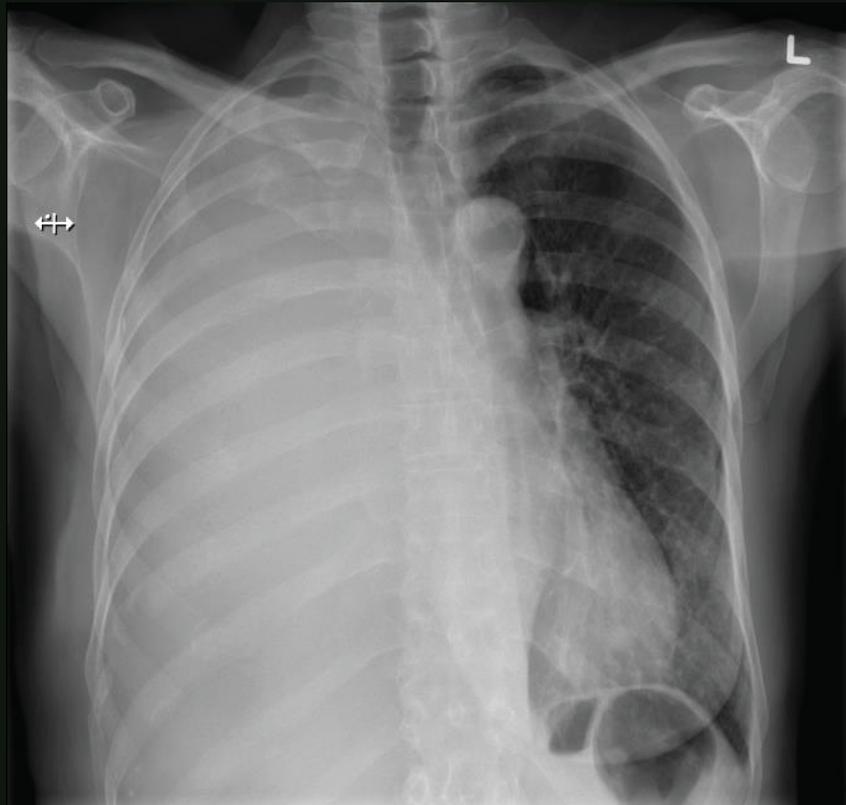
Conclusions:

- Clinical and radiographic RPE after large volume thoracentesis is rare and independent of the volume of fluid removed, pleural pressures, and pleural elastance.
- The recommendation to terminate thoracentesis after removing 1 L of fluid needs to be reconsidered
- Large effusions can, and should, be drained completely as long as chest discomfort or end-expiratory pleural pressure less than 20 cm H₂O does not develop.

Feller-Kopman D, et.al. Ann Thorac Surg 2007;84:1656-62.

Re-expansion Pulmonary Edema Guidelines

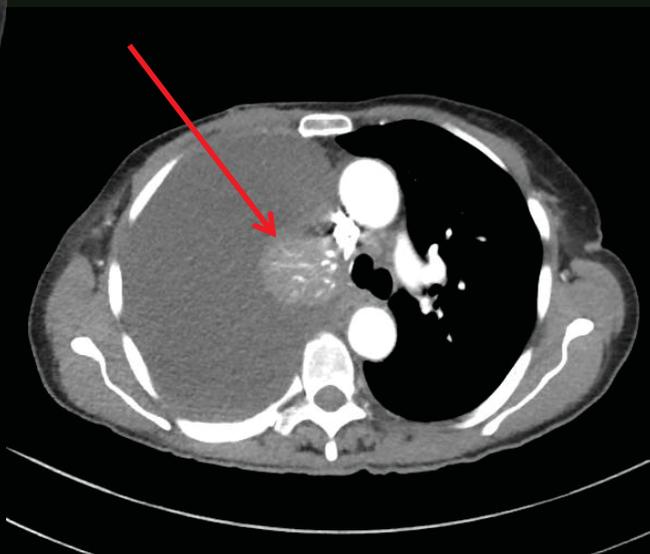
- Incidence of 0-1%
- Most suggest drainage of 1.5 L or less, though some suggest more can be drained, provided no respiratory symptoms occur
- Avoid excessive negative pressure
- Higher Risk: Large pneumothoraces, Younger age, Hx of > 7 days, Fluid amounts of > 3 L

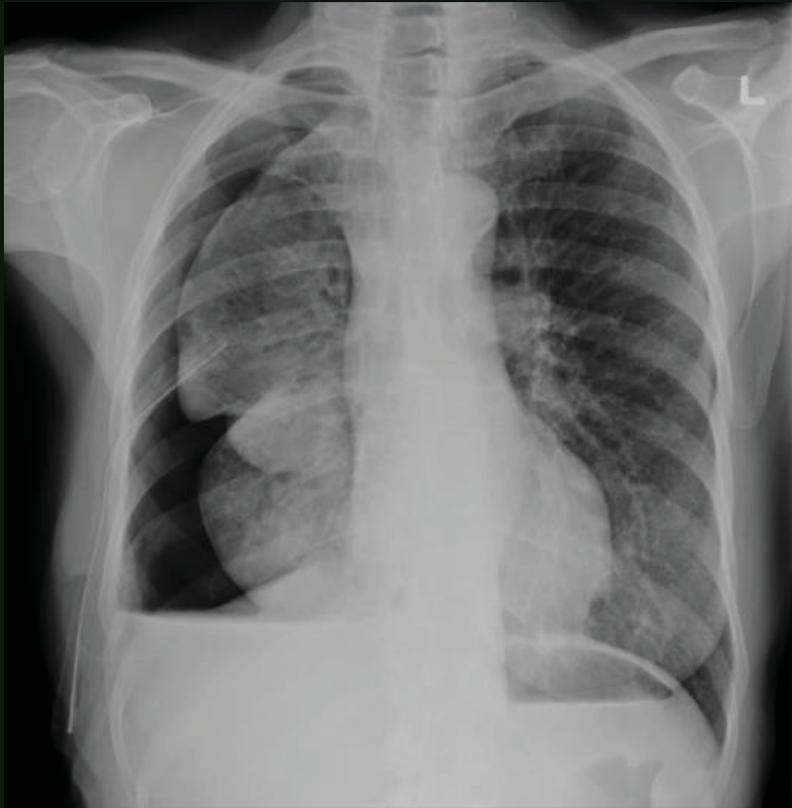


Other Considerations Longstanding Effusions



Other Considerations Longstanding Effusions





My personal approach...

- RPO happens in 0-1%; be aware of that
- Stop when patients become symptomatic, or just before, often around 1.5-2 litres
- Consider repeating the procedure in 24-48 hours if significant fluid remains
- Beware of the longstanding large effusion

Do I have to keep draining this?

Can one get rid of the recurrent effusion?

Malignant Pleural Effusion Effectiveness of Therapeutic Options (percent resolution)

- | | |
|--|--------|
| • Therapeutic thoracenteses | 0 |
| • Indwelling pleural catheter | 40-70 |
| • Chest tube drain | 10-30 |
| • Chest tube drain with talc slurry | 60-64 |
| • VATS with talc poudrage | 75-87 |
| • VATS with pleural abrasion / pleurectomy | 93-100 |
| • Pleuroperitoneal shunt | 95 |

Management Approach to Dyspnea

Identify and treat underlying causes if possible and if appropriate

Treat the dyspnea

Communicate with the patient as possible, and with the family, explaining the situation and the plan

Non-pharmacological Management of Dyspnea

- Avoid exacerbating activities & conserve energy
- Normalize emotional responses to dyspnea
- Use a fan
- Position: lean forward, head up
- Limit people in room
- Reduce room temperature,
- Maintain humidity
- Open window for air and sight
- Avoid irritants e. g. smoke
- Relaxation therapy

What is the role of oxygen
in the management
of dyspnea?

Oxygen Therapy - COPD

- 1995: nearly 800,000 patients receiving long-term oxygen therapy in the United States, at a yearly cost of \$1.8 billion*
- Associated with improvements in survival, quality of life, and neuro-psychologic function in patients with COPD and hypoxia

* Tarpy SP, Celli BR. *LONG-TERM OXYGEN THERAPY*. NEJM (1995): 333:710-714.

Early Oxygen Studies

- 1993 – Bruera
 - Randomized double-blind crossover trial in 14 patients with advanced cancer and hypoxemia based on $SAO_2 < 90\%$
 - Oxygen vs air at 5L/min
 - ❖ Average dyspnea by VAS significantly less in patients receiving Oxygen

Early Oxygen Studies

- 1994 – Booth
 - Single-blind crossover trial of oxygen and air in random order to 38 hospice patients reporting dyspnea at rest
 - Mixed hypoxic and non-hypoxic
 - Both groups had a significant improvement of dyspnea on VAS scores
- ❖ No statistical significance between the two treatments

Oxygen vs Air for Patients with Cancer and Dyspnea

- Randomized, double-blind, crossover study in Australia
- Primary aim:
 - to determine blinded patient preference for oxygen or air, following 15-minute administration of both.
- Secondary aims:
 - to compare the response to oxygen and air in hypoxic and normoxic patient groups,
 - to identify factors other than hypoxia that may affect the experience of dyspnea and the response to oxygen.

Oxygen vs Air for Patients with Cancer and Dyspnea

- Blinded trial for 51 patients and investigators
- Used VAS and EORTC Dyspnea Measurement



Philip et.al. A Randomized, Double-Blind, Crossover Trial of the Effect of Oxygen on Dyspnea in Patients with Advanced Cancer. J Pain Symptom Manage 2006;32:541-550

Oxygen vs Air for Patients with Cancer and Dyspnea

Oxygen Saturation:

- Significant improvement in the group receiving Oxygen (5.43%) vs the group receiving air (0.94%)

Gas Preference:

- 21 (41%) patients preferred Oxygen
- 15 (29%) patients preferred air
- 15 (29%) patients expressed no preference

(P=0.357 – not significant)

Philip et.al. A Randomized, Double-Blind, Crossover Trial of the Effect of Oxygen on Dyspnea in Patients with Advanced Cancer. J Pain Symptom Manage 2006;32:541-550

Oxygen vs Air for Patients with Cancer and Dyspnea

Hypoxic Group:

- 17 patients
- Mean SAO₂ increased by 10.7% with Oxygen and 2.7% with air ($p=0.005$)
- Mean change in VAS score increased by 15.4 mm with air and 13.3 mm with oxygen ($p=0.812$)
- 35 % expressed preference for air, 24 % for oxygen and 41 % had no preference

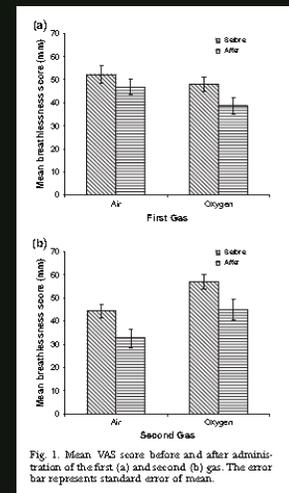


Fig. 1. Mean VAS score before and after administration of the first (a) and second (b) gas. The error bar represents standard error of mean.

Philip et.al. A Randomized, Double-Blind, Crossover Trial of the Effect of Oxygen on Dyspnea in Patients with Advanced Cancer. J Pain Symptom Manage 2006;32:541-550

Oxygen vs Air for Patients with Cancer and Dyspnea

- Dyspnea in advanced cancer is the expression of multiple sensations and experiences, and not simply related to oxygen tension
- Both oxygen and air administered intranasally improve the mean sensation of dyspnea for patients with advanced cancer
- No significant difference between the gases in either VAS or preferences expressed
- The role of oxygen to relieve dyspnea in advanced cancer may require further investigation, with particular attention given to longer-term studies

Philip et.al. A Randomized, Double-Blind, Crossover Trial of the Effect of Oxygen on Dyspnea in Patients with Advanced Cancer. J Pain Symptom Manage 2006;32:541-550

Does palliative home oxygen improve dyspnoea?

- Consecutive cohort study
- Aim: to define any symptomatic benefit of the provision of home oxygen measured by routine recording of breathlessness with each clinical encounter within a specialist community palliative care team.
- Mean SAS for breathlessness was 5.4 before oxygen and 5.2 approximately 2 weeks after oxygen initiation
($p=0.35$ – not significant)

Currow DC et.al. Does palliative home oxygen improve dyspnoea?
A consecutive cohort study. Palliative Medicine 2009; 23: 309–316

Patients' experience of oxygen therapy and dyspnea

- Perceived advantages:
 - Increased ambulation
 - Improved participation in activities such as cleaning, reading, shaving
 - Improved nausea, appetite and skin color

Jaturapatporn D et.al. Patients' experience of oxygen therapy and dyspnea: a qualitative study in home palliative care. Support Care Cancer (2010) 18:765–770.

Patients' experience of oxygen therapy and dyspnea

- Perceived disadvantages:
 - Mobility and safety related to the Oxygen tubing
 - Difficulty transporting the tank and difficulty using a walker with an oxygen tank (more modern equipment helped)
 - Discomfort in the nasal cavity and ears related to nasal prongs.
 - Noise related to the equipment
 - Access to oxygen difficult if SAO₂ not low enough

Jaturapatporn D et.al. Patients' experience of oxygen therapy and dyspnea: a qualitative study in home palliative care. Support Care Cancer (2010) 18:765–770.

Role of Oxygen in Dyspnea

- Mechanism: unclear
- What is helping?
 - Oxygen, airflow, placebo, something else?
- O₂ in hypoxic cancer patients may be useful
- O₂ in non-hypoxic cancer patients has not been shown to be useful; airflow may be as helpful

What medications are most useful in managing dyspnea in palliative care?

Oxygen and opioids in the palliation of dyspnoea

- Purpose: to determine effects of oxygen and opioid treatment on ventilation and relief of dyspnoea in hypoxic and non-hypoxic palliative care patients, both opioid-naïve or pre-treated with strong opioids.
- Included if they had
 - advanced, terminal cancer or other terminal incurable disease
 - dyspnoea at rest
 - normal cognitive status
 - Hgb \geq 100
- Excluded if they had
 - non-compensated CHF
 - severe renal or hepatic failure
 - other uncontrolled symptoms that could require the use of opioids.

Oxygen and opioids in the palliation of dyspnoea

- 46 patients
- No significant differences between hypoxic and non-hypoxic patients with regard to Oxygen or opioids for dyspnea
- Neither hypoxic nor non-hypoxic patients had a beneficial effect from Oxygen at rest

Clemens KE et.al. Use of oxygen and opioids in the palliation of dyspnoea in hypoxic and non-hypoxic palliative care patients: a prospective study. Support Care Cancer (2009) 17:367–377

Oxygen and opioids in the palliation of dyspnea

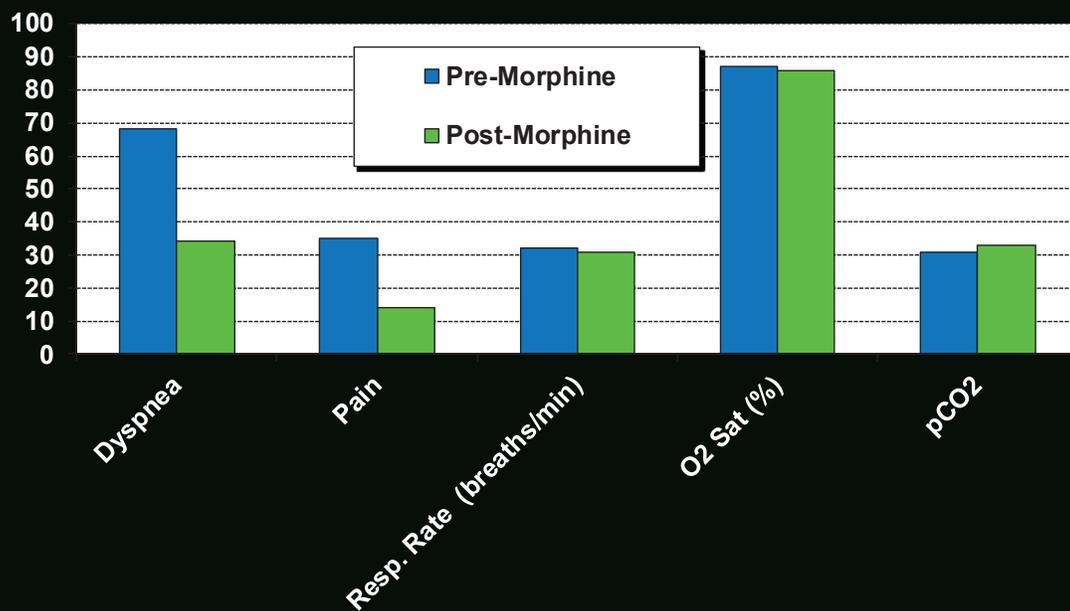
Opioids worked significantly better than oxygen in reducing the intensity of dyspnea, both in hypoxic and non-hypoxic patients.

Clemens KE et.al. Use of oxygen and opioids in the palliation of dyspnoea in hypoxic and non-hypoxic palliative care patients: a prospective study. Support Care Cancer (2009) 17:367–377

Does the use of opioids hasten death?

NO

Subcutaneous Morphine in Terminal Cancer

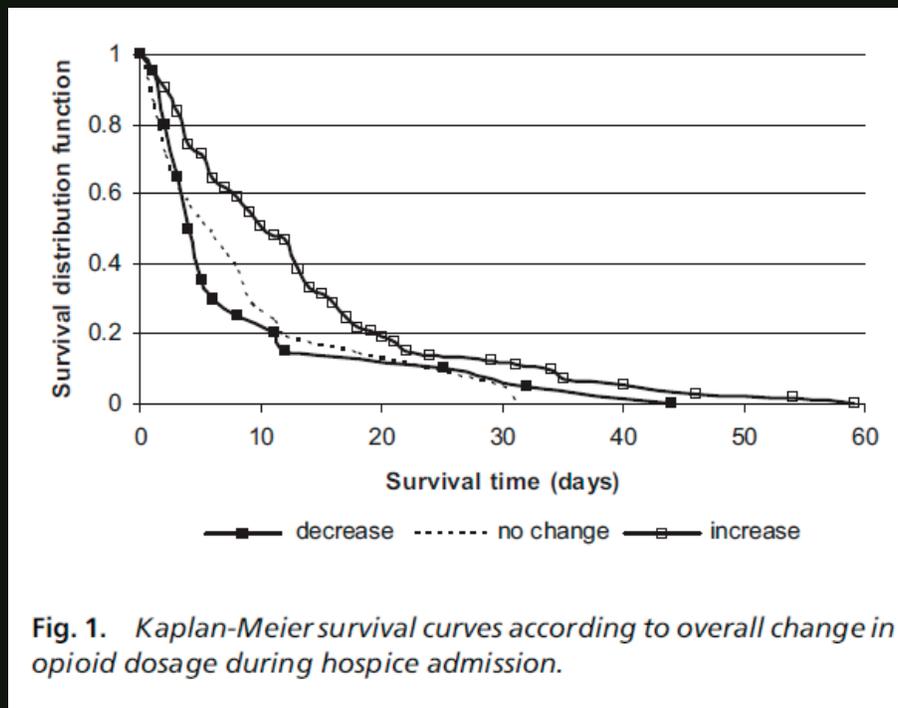


Opioids, Survival and Advanced Cancer in the Hospice Setting

- 114 consecutive hospice patients, ages 13-71
- Analysis of survival, according to opioid use
- No significant relationship found between mortality and:
 - Dose on admission
 - Dose at death
 - Mean dose
 - Overall dose increase and decrease
 - Day by day dosage changes

Azoulay D, et.al. J Am Med Dir Assoc 2011;12:129-34

Opioids, Survival and Advanced Cancer in the Hospice Setting



Azoulay D, et.al. J Am Med Dir Assoc 2011;12:129-34

Opioids for Dyspnea

- *There is low quality evidence showing benefit for the use of oral opioids for the relief of breathlessness in some adults with advanced disease and terminal illness.*
- *Based on this evidence, it is possible that opioids lead to a short-term increase in exercise capacity.*
- *It is difficult to draw firm conclusions about the clinical significance of the pooled estimate of treatment effect ... but the magnitude of the treatment effect appears small.*
- *There is no evidence to support the use of nebulised opioids for the treatment of breathlessness.*

Barnes H, et.al. Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness. Cochrane Database of Systematic Reviews 2016, Issue 3. Art. No.: CD011008.

Fentanyl for Relief of Refractory Breathlessness

- Small studies
- All reported successful relief of breathlessness after fentanyl
- The only RCT failed to demonstrate a statistically significant difference compared with placebo.
- The nature and incidence of adverse events were comparable with other opioids; no respiratory depression was observed
- Conclusion: Descriptive studies yielded promising results for the use of fentanyl for the relief of breathlessness; however, efficacy trials are lacking

Simon S, et.al. Fentanyl for the Relief of Refractory Breathlessness: A Systematic Review. J Pain Symptom Manage 2013;46:874e886.

Episodic Breathlessness

- Resembles incident pain
- Severe intensity, short duration, often predictable and often induced by a recognizable cause
- Best treated with substances with rapid onset and short duration of action
- Try to prevent or preempt its occurrence
 - Optimization of persistent dyspnea
 - Treatment of psychologic and environmental causes

Mercaqndante, S. Episodic Breathlessness in Patients with Advanced Cancer: Characteristics and Management. *Drugs* (2018) 78:543–547

Steroids for Breathlessness

There is insufficient evidence to support or refute the suggestion that systemic corticosteroids have any efficacy in cancer-related breathlessness (dyspnoea) in adults. This may be particularly relevant when considering the potential toxicity of corticosteroids, especially following prolonged use.

Haywood A, et.al. Systemic corticosteroids for the management of cancer-related breathlessness (dyspnoea) in adults (Review). *Cochrane Database of Systematic Reviews* 2019, Issue 2. Art. No.: CD012704.

Midazolam for Breathlessness

- randomised double-blind, multi-dose, placebo controlled study in patients with dyspnoea related to life-limiting disease
- Intranasal: 0.5 mg midazolam vs placebo
- Assessed at 5, 15, 30 and 60 minutes post administration
- No meaningful benefit on dyspnoea or anxiety for midazolam when compared to placebo.

Hardy J, et.al. A randomised, double-blind controlled trial of intranasal midazolam for the palliation of dyspnoea in patients with life-limiting disease. Support Care Cancer (2016) 24:3069–3076.

Midazolam as Adjunct Therapy

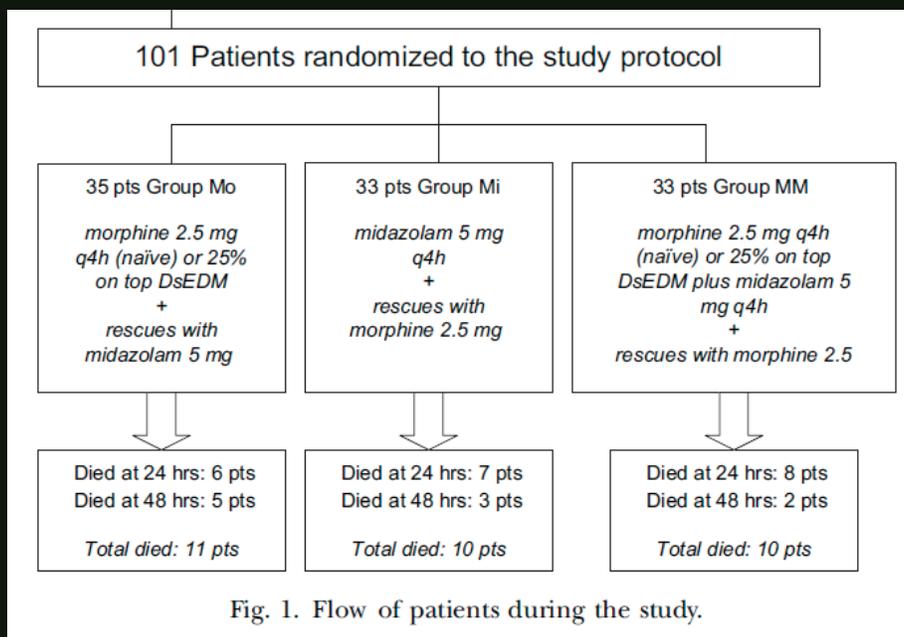


Fig. 1. Flow of patients during the study.

Navigante AH, et.al. Midazolam as Adjunct Therapy to Morphine in the Alleviation of Severe Dyspnea Perception in Patients with Advanced Cancer. J Pain Symptom Manage 2006;31:38--47.

Midazolam as Adjunct Therapy

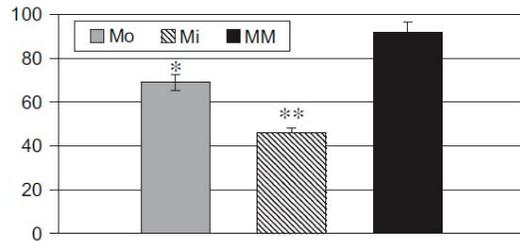


Fig. 2. Percentage of patients who experienced dyspnea relief at 24 hours. * $P=0.003$ compared with MM. ** $P=0.0004$ compared with MM.

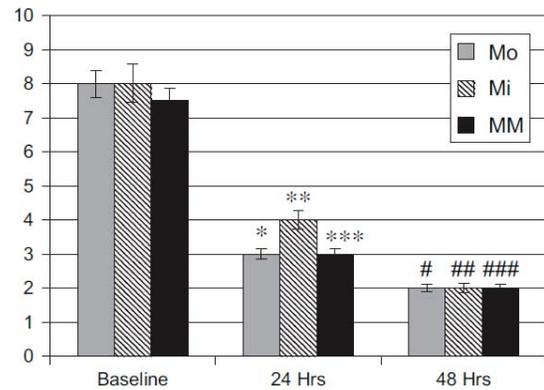


Fig. 3. Dyspnea intensity (Borg scale) at 24 and 48 hours (median). * $P=0.002$, ** $P=0.018$, *** $P=0.003$ compared with their respective baseline values. # $P=0.0001$, ## $P=0.0004$, ### $P<0.0001$ compared with their respective baseline values.

Navigante AH, et al. Midazolam as Adjunct Therapy to Morphine in the Alleviation of Severe Dyspnea Perception in Patients with Advanced Cancer. J Pain Symptom Manage 2006;31:38--47.

Midazolam as Adjunct Therapy

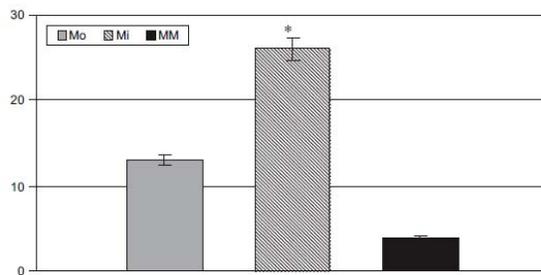


Fig. 4. Percentage of patients with persistent, uncontrolled dyspnea at 48 hours. * $P=0.04$ compared with MM.

Persistent, uncontrolled dyspnea at 48 hours

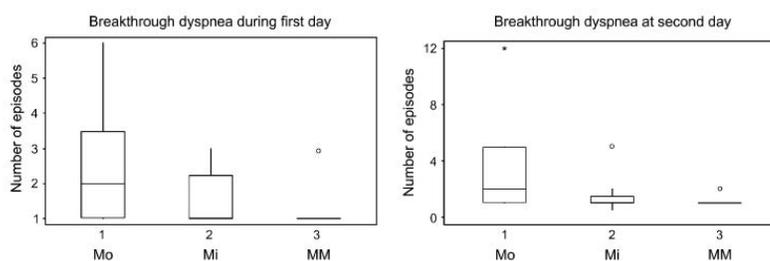


Fig. 5. Episodes of BD.

Breakthrough dyspnea at first and second days

Navigante AH, et al. Midazolam as Adjunct Therapy to Morphine in the Alleviation of Severe Dyspnea Perception in Patients with Advanced Cancer. J Pain Symptom Manage 2006;31:38--47.

Other Adjuvant Medications for Dyspnea ? Consider the Circumstances

- Methotrimeprazine 2.5-12.5mg bid-tid
- Lorazepam or clonazepam 0.5-1mg q6-8hr
 - only if anxiety is causal factor
- Bronchodilators (if bronchoconstriction is a factor)
- Furosemide – CHF, pulmonary edema

Ms. P

- Ms. P is 42 years old, hospitalized with advanced sarcoma. She has multiple metastatic lesions in her lungs and occasional hematemesis. She has a history of recurrent DVT and pulmonary emboli. She has significant exertional dyspnea, limiting her to bed, with occasional assisted trips to the bathroom.
- Currently she is on daily Coumadin, her last INR was 1.5 four days ago.
- She becomes acutely short of breath.

Severe Dyspnea in Last Hours of Life

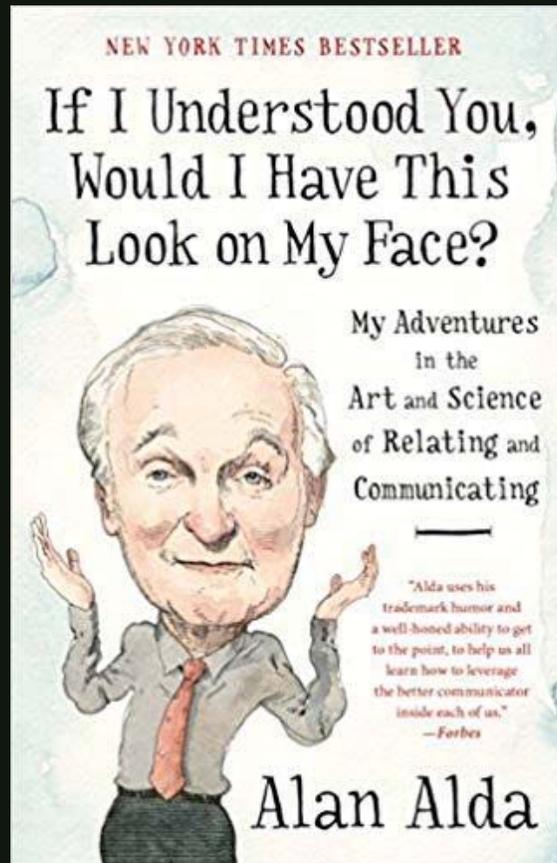
- Opioid naïve
 - 2.5-5mg morphine IV/SC stat then reassess
- Opioid tolerant
 - 25-100% increase in dose IV/SC stat
- Midazolam 5-10 mg intranasal
- Intractable dyspnea
 - Add Methotrimeprazine
 - Consider palliative sedation (e.g. midazolam infusion – remember bolus dose)

Management Approach to Dyspnea

Identify and treat underlying
causes if possible and if
appropriate

Treat the
dyspnea

Communicate with the
patient as possible, and
with the family, explaining
the situation and the plan



Summary

- Breathlessness affects quality of living and can be very distressing to the patient and family
- Consider interventions directed at underlying causes
- Oxygen is likely to be minimally effective as a treatment, except in hypoxia
- Treatment of breathlessness with opioids is safe and effective
- Midazolam may be a helpful adjunct
- Severe dyspnea at the end of life demands aggressive treatment