



Symptom Management When Death is Imminent Fast Facts and Concepts and CME Module

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FAST FACTS AND CONCEPTS: CONTINUING MEDICAL EDUCATION MODULE
SYMPTOM MANAGEMENT WHEN DEATH IS IMMINENT
COURSE DESCRIPTION AND LEARNING OBJECTIVES

Course Description: Clinicians who care for patients with chronic and progressive illness need to acquire a core competency in recognizing when patients are dying and managing common symptoms from the dying process in an effective and ethical manner. Major medical groups such as the American Medical Association (AMA), the American College of Physicians (ACP), and the National Consensus Project for Quality Palliative care have highlighted these core patient care skills for generalist clinicians. Unless a clinician can diagnose a dying process, an opportunity to provide the appropriate care for a dying patient will be missed. In this module, users will learn about the prognostic significance of numerous clinical signs and symptoms common in dying patients, as well as evidence-based strategies for managing these symptoms. Upon completion of this module, users can attain 1.0 hours of CME credit by completing the following tasks:

- A. Review the content of 10 Fast Fact and Concepts relevant to the topic of Symptom Management when Death is Imminent on the following topics –
 - a. Terminal delirium
 - b. Syndrome of Imminent Death
 - c. Dyspnea
 - d. Nightmares
 - e. Diarrhea
 - f. Death Rattle
 - g. Myoclonus
 - h. Nonoral hydration decisions at the end of life
 - i. Fever
 - j. Thirst
- B. Attain a score of 70% or higher on a 10 question post-content quiz covering the educational content presented.
- C. Completion of a course evaluation.

Learning Objectives: After completion of this 1.0 hour CME course, the learner will be able to:

1. Describe cardinal features of the early, middle, and late stages of imminent death.
2. Anticipate common family concerns and questions about the management of the dying process.
3. Utilize effective pharmacologic and non-pharmacologic therapies for at least 8 symptoms common to imminently dying patients.

FAST FACTS AND CONCEPTS #001
DIAGNOSIS AND TREATMENT OF TERMINAL DELIRIUM

David E Weissman MD and Drew A Rosielle MD

Background Some degree of loss of cognitive function occurs in most patients in the week or two before death. The typical scenario presented to housestaff is a late-night call from a ward nurse saying, “*Mr. Jones is confused, what should we do?*” This *Fast Fact* reviews assessment and management issues in terminal delirium. See *Fast Fact* #60 for a discussion of newer pharmacological treatments.

Key teaching points:

1. The term “confusion” is not an accurate descriptive term—it can mean anything from delirium, dementia, psychosis, obtundation, etc. Patients need a focused assessment, including a brief mini-mental examination. Clinicians should use one of several validated delirium assessment tools to help quantify and document cognitive function.
2. “Terminal delirium” is not a distinct diagnosis, although it is a commonly used phrase. It implies delirium in a patient in the final days/weeks of life, where treatment of the underlying cause is impossible, impractical, or not consistent with the goals of care.
3. Delirium can be either a *hyperactive/agitated delirium* or a *hypoactive delirium*. The hallmark of delirium is an acute change in the level of arousal; supporting features include altered sleep/wake cycle, mumbling speech, disturbance of memory and attention, and perceptual disturbances with delusions and hallucinations.
4. The most common identifiable cause of delirium in the hospital setting is drugs: anti-cholinergics (e.g. anti-secretion drugs, anti-emetics, anti-histamines, tricyclic anti-depressants, etc.), sedative-hypnotics (e.g. benzodiazepines), and opioids. Other common causes include metabolic derangements (elevated sodium or calcium, low glucose or oxygen); infections; CNS pathology; or drug/alcohol withdrawal.
5. The degree of work-up to seek the cause of delirium is determined by understanding the disease trajectory and overall *goals of care* (see *Fast Fact* #65).
6. The drug of choice for most patients is a neuroleptic. There is one controlled clinical trial of haloperidol versus lorazepam in HIV patients; haloperidol was the superior agent. Haloperidol is administered in a dose escalation process similar to treating pain. Start haloperidol 0.5-2 mg PO or IV q1hour PRN. Atypical antipsychotics have also been studied for delirium and are probably as efficacious as haloperidol. There are insufficient data to make a strong recommendation about the best drug or dosing of antipsychotics for delirium.
7. It is best to think of benzodiazepines as *sedatives* and *anxiolytics* but not as therapy for underlying delirium. On the rare occasion one wants to actually *sedate* a delirious patient a benzodiazepine may be indicated. If anxiety is a prominent part of a patient’s delirium, a benzodiazepine may help. Generally, however, benzodiazepines should be avoided as they can cause paradoxical worsening of the delirium and agitation.
8. Non-pharmacological treatments should always be used in delirium management: reduce or increase the sensory stimulation in the environment as needed; ask relatives/friends to stay by the patient; frequent reminders of time/place.

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FAST FACTS AND CONCEPTS #3 SYNDROME OF IMMINENT DEATH

David E Weissman MD

Background Virtually all dying patients go through a stereotypical pattern of symptoms and signs in the days prior to death. This trajectory is often referred to as "actively dying" or "imminent death". Prompt recognition of this trajectory is key for clinicians to provide the most appropriate interventions for both the patient and family.

1. Stages

- **Early**
 - Bed bound
 - Loss of interest and/or ability to drink/eat
 - Cognitive changes: increasing time spent sleeping and/or delirium (see *Fast Fact #1*)
- **Middle**
 - Further decline in mental status to obtundation (slow to arouse with stimulation; only brief periods of wakefulness)
- **Late**
 - Death rattle – pooled oral secretions that are not cleared due to loss of swallowing reflex
 - Coma
 - Fever – usually from aspiration pneumonia
 - Altered respiratory pattern – periods of apnea, hyperpnea, or irregular breathing
 - Mottled extremities

2. Time Course The time to traverse the various stages can be less than 24 hours or as long as ~14 days. Patients who enter the trajectory who are nutritionally intact, with no infection (e.g. acute stroke), are apt to live longer than cachectic cancer patients

3. Common Family Concerns Family members present during the dying process often express the following concerns/questions. Clinicians can best help families by expecting these questions, providing education, reassurance, and responding to emotions (see also *Fast Fact # 29; #149*).

- Is my loved one in pain; how would we know?
- Aren't we just starving my loved one to death?
- What should we expect; how will we know that time is short?
- Should I/we stay by the bedside?
- Can my loved one hear what we are saying?
- What do we do after death?

4. Treatment

- Confirm treatment goals; recommend stopping treatments that are not contributing to comfort – pulse oximetry, IV hydration, antibiotics, finger sticks, etc.
- Communicate clearly to others what is going on. Write in progress notes: "patient is dying," not "prognosis is poor".
- Treat symptoms/signs as they arise: common among these are: oral secretions (see *Fast Fact #109, #158*); delirium (#1, 60); dyspnea (# 27), fever (#256) and pain (# 53, 54).
- Provide excellent mouth and skin care.
- Provide daily counseling and support to families.

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FAST FACTS AND CONCEPTS #27 DYSPNEA AT END-OF-LIFE

David E Weissman MD

Introduction Dyspnea is defined as a subjective sensation of difficulty breathing. This *Fast Fact* reviews key elements in the assessment and treatment of dyspnea near the end-of-life.

Etiology The causes of dyspnea include a wide spectrum of serious lung or heart conditions, anemia, anxiety, chest wall pathology, electrolyte disturbances or even urinary retention or constipation.

Assessment Looking for simple problems is always warranted: is the Oxygen turned on? Is the tubing kinked? Is there fluid overload from IV fluids or TPN? Is dyspnea part of an acute anxiety episode, severe pain, constipation or urinary retention? Is there a new pneumothorax or worsening pleural effusion? Understanding 1) where patients are at in the dying trajectory, and 2) their identified goals of care, is essential to guide the extent of workup to discover reversible causes. If the patient is clearly dying (see *Fast Fact #3*), and the goals of care are comfort, then pulse oximetry, arterial blood gases, EKG, or imaging are not indicated.

Treatment

- **General measures** Positioning (sitting up), increasing air movement via a fan or open window, and use of bedside relaxation techniques are all helpful. In the imminently dying patient, discontinuing parenteral fluids is appropriate.
- **Treatment with opioids** Opioids are the drugs of choice for dyspnea at the end-of-life as well as dyspnea refractory to the treatment of the underlying cause. In the opioid naïve patient, low doses of oral (5-10 mg) or parenteral morphine (2-4 mg) will provide relief for most patients; higher doses will be needed for patients on chronic opioids. When dyspnea is acute and severe, parenteral is the route of choice: 1-3 mg IV every 1-2 hours, or more aggressively if needed, until relief in the opioid naïve patient. In the inpatient setting, a continuous opioid infusion, with a PCA dose that patients, nurses or families can administer, will provide the timeliest relief (see *Fast Facts #28, 54*). Nebulized morphine has been reported to provide benefit in uncontrolled case reports, however a controlled trial demonstrated no greater efficacy or lower rate of side effects compared to subcutaneous morphine.
- **Treatment with oxygen** Oxygen is often, but not universally, helpful. When in doubt, a therapeutic trial, based on symptom relief, not pulse oximetry, is indicated in dying patients. A well-designed randomized, controlled trial of oxygen vs ambient air, delivered by nasal cannula, in normoxic patients with advanced illness and dyspnea showed no benefit of oxygen over ambient air delivered by nasal cannula. Patients generally prefer nasal cannula administration than a mask, especially in setting of imminent death when agitation from the mask is commonly seen. There is little reason to go beyond 4-6 L/min of oxygen via nasal cannula in the actively dying patient. Request a face-tent for patients who are claustrophobic from a mask.
- **Treatment with other drugs** Anti-tussives can help with cough (see *Fast Fact #200*), anticholinergics (e.g. scopolamine) will help reduce secretions, anxiolytics (e.g. lorazepam) can reduce the anxiety component of dyspnea. Other agents that may have specific disease modifying effects include diuretics, bronchodilators, and corticosteroids.

Family/Team Discussions While there is no evidence that proper symptom management for terminal dyspnea hastens death, the course and management of terminal dyspnea, especially when opioids are

used, should be fully discussed with family members, nurses and others participating in care to avoid confusion about symptom relief vs. fears of euthanasia or assisted suicide (see *Fast Fact #8*).

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FAST FACTS AND CONCEPTS #88
NIGHTMARES
Seema Malhotra MD, Robert Arnold MD, and Kevin Patterson MD

Background Good, restful sleep is essential to quality of life – providing renewed energy for the next day. Nightmares are vivid, frightening dreams that typically lead to full awakening with detailed recollection of the dream sequence and content. Following a nightmare, heart rate and blood pressure are elevated, and residual anxiety may interfere with the ability to return to sleep. Nightmares occur almost exclusively during REM (Rapid Eye Movement) sleep.

Causes

- *Psychiatric.* Anxiety is a common symptom during a life-threatening illness. Specifically, anxieties related to the illness course and prognosis, procedures and treatments, family issues, and death, can be significant. Nightmares may arise as a complication of anxiety or other psychiatric disturbances (such as post-traumatic stress disorder, delirium, mood disorders, schizophrenia, and adjustment disorders).
- *Medications/Drugs/Alcohol.* Medications causally linked to nightmares include: beta-blockers, sedative/hypnotics, amphetamines and other stimulants, dopamine agonists, and antidepressants. Withdrawal from REM-suppressing drugs, including antidepressants, benzodiazepines, and alcohol, predisposes to the development of nightmares.
- *Brain disorders.* CNS infections, brain tumors and other structural problems of the brain may lead to nightmares.
- *Metabolic:* hypoglycemia.

Psychotherapeutic Interventions can be particularly helpful for people whose nightmares are related to stress/anxiety or an underlying psychiatric condition.

- *Supportive Psychotherapy.* Brief, supportive psychotherapy can address a patient's anxieties and concerns; the therapist helps the patient with problem solving, seeking information and support, and accepting aspects of their situation which cannot be changed.
- *Behavioral techniques.* Relaxation training, desensitization, and dream imagery rehearsal therapy may help reduce nightmares. In imagery rehearsal therapy, the patient writes down the disturbing dream, changes the content, and practices the new, positive scenario mentally during the day; this new imagery during the day reduces nightmares at night.

Pharmacologic Management The pharmacologic treatment of nightmares has not been studied in controlled clinical trials. Case studies and anecdotal reports suggest the following drugs or drug classes may be effective:

- *Atypical Antipsychotics:* risperidone (0.5-2 mg qhs) and olanzapine (5 mg) have both been shown to reduce nightmares in small pilot studies of patients with acute stress and PTSD, including reduction in flashbacks, hyperarousal, and disturbed sleep.
- *Alpha-1 Antagonists:* prazosin (2-15 mg qhs) has been shown to reduce nightmares and other sleep-related symptoms in PTSD patients in multiple small studies and a single randomized controlled trial involving 13 patients.
- *Benzodiazepines and Tricyclic Antidepressants* may be of benefit in suppressing REM activity. Note: trazadone does not suppress REM activity.
- *Other:* Both cyproheptadine and topiramate have been reported to suppress nightmares in small case series.

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FAST FACTS AND CONCEPTS #96
DIARRHEA IN PALLIATIVE CARE
Jeffrey Alderman MD

Diarrhea is a debilitating and embarrassing problem, defined as an abnormal looseness of the stools (increased liquidity or decreased consistency). Patients with uncontrolled diarrhea are at increased risk for dehydration, electrolyte imbalance, skin breakdown, and fatigue.

Common Causes Diarrhea can usually be divided into different types and treatment will vary depending on cause: secretory, osmotic, mechanical, or disordered motility. In palliative care, the overuse of laxatives, typically seen when the management of constipation is suddenly 'stepped-up,' is a common cause. Other causes include partial intestinal obstruction, pancreatic insufficiency, *Clostridium difficile* infection, and radiation enteritis. Chemotherapeutics are another common cause, especially in advanced cancer where the incidence can be up to 60% (diarrhea may be even more common with chemotherapy regimens with 5 fluorouracil boluses or combination of irinotecan and fluoropyrimidines). Infectious diarrhea is especially common in HIV infection (*Cryptosporidium*, *Giardia lamblia*, *E. histolytica*, and Cytomegalovirus). Severe constipation and fecal impaction can also cause diarrhea as backed-up, liquefied stool may be all that the patient can pass ('overflow diarrhea').

Evaluation Review diet, medications, laxatives, procedures, timing of movements in relation to ingestion of food or liquids, and a description of quantity and quality of stool. When performing a physical exam, make sure to palpate the abdomen and do a rectal exam. Radiographs are often not necessary, but may help clarify a partial bowel obstruction or overflow diarrhea. Keep in mind that patients at the end-of-life are also at risk for developing the same diarrheal illnesses that occur in the general population (viral/bacterial gastroenteritis, adverse effects of medications).

Treatment

- **General** Ensure adequate hydration; encourage sips of clear liquids; parenteral hydration should be considered for severe dehydration. Simple carbohydrates, toast or crackers, will add back small amounts of electrolytes and glucose; milk and other lactose-containing products should be avoided.
- **Medications** include bulk forming agents, antimicrobials, adsorbents, and opioids.
 - **Kaolin and Pectin** (Kaopectate®) is a suspension of adsorbent and bulk-forming agents, which can provide modest relief from diarrhea. However, kaolin-pectin may take up to 48 hours to produce an effect and can interfere with the absorption of certain medications.
 - **Antibiotics:** infectious diarrhea should be identified and treated with appropriate antibiotics, particularly *C. difficile* enteritis.
 - **Bismuth** has an additional antimicrobial effect, and can be added for increased symptomatic control against organisms such as enterotoxigenic *E. Coli*.
 - **Loperamide** (Imodium®), an opioid, reduces peristalsis in the gut, increases water reabsorption, and promotes fecal continence, making it a potent anti-diarrheal agent. Because it only weakly crosses the blood-brain barrier, loperamide's side effect profile is more favorable than other opioids (e.g. codeine or diphenoxylate [Lomotil®]). The initial dose of loperamide is 4 mg, with titration to 2 mg after each loose stool, with the typical dose being 4 – 8 mg per day. Although the package insert recommends a maximum of 16 mg in a 24-hour period, up to 54 mg per day of loperamide has been used in palliative care settings with few adverse effects. Note: loperamide should be used with caution if an infectious diarrhea is suspected.
 - **Aspirin and Cholestyramine** can reduce the diarrhea in radiation-induced enteritis, as can addition of a stool bulking agent such as psyllium (Metamucil™).
 - **Mesalamine** and other antiinflammatories are used for inflammatory bowel disease.
 - **Pancreatic Enzymes** such as pancrelipase are used for pancreatic insufficiency.
 - **Octreotide**, although costly, is effective with profuse secretory diarrhea seen in HIV disease, chemotherapy induced diarrhea, and those with high effluent volume from a stoma. It may be given via continuous subcutaneous infusion at a rate of 10 – 80 mcg every hour until symptoms improve.
 - **Budesonide, probiotics and activated charcoal** have been described in the literature for use in chemotherapy induced diarrhea, but their role in the clinical setting is not yet established.

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FAST FACTS AND CONCEPTS #109
DEATH RATTLE AND ORAL SECRETIONS
Kathleen Bickel and Robert Arnold MD

Background As consciousness decreases in the dying process, patients lose their ability to swallow and clear oral secretions. Air moves over the secretions, which have pooled in the oropharynx and bronchi, resulting in turbulence and noisy ventilation with each breath. This is often described as 'gurgling' or 'rattling noises.' While there is no evidence that patients find this 'death rattle' disturbing, evidence from bereaved surveys suggests the noises can be disturbing to the patient's visitors and caregivers who may fear that the patient is choking to death. Similar sounds may occur in patients who are not imminently dying, such as in those with brain injuries or in disorders like Amyotrophic Lateral Sclerosis in which increased production or decreased clearance of secretions occurs. Two sub-types of the death rattle have been proposed, although the significance regarding treatment has not been established: Type 1 = predominantly salivary secretions and Type 2 = predominantly bronchial secretions. Death rattle is a good predictor of near death; one study indicated the median time from onset of death rattle to death was 16 hours.

Non-Pharmacological Treatments

- Position the patient on their side or in a semi-prone position to facilitate postural drainage
- A minute or two of Trendelenburg positioning can be used to move fluids up into the oropharynx for easier removal; aspiration risk is increased, however.
- Gentle oropharyngeal suctioning is used although this can be ineffective when fluids are beyond the reach of the catheter. Frequent suctioning is disturbing to both the patient and the visitors.
- Reduction of fluid intake.
- Communication with family and caregivers aimed to address associated fears and interpretations.

Pharmacological Treatments While multiple studies have questioned the utility of pharmacologic treatments for death rattle, muscarinic receptor blockers (anti-cholinergic drugs) are the most commonly used class of medication for this symptom. Such agents include scopolamine, hyoscyamine, glycopyrrolate, and atropine. All of these agents can cause varying degrees of blurred vision, sedation, confusion, delirium, restlessness, hallucinations, palpitations, constipation, and urinary retention. The primary difference in these drugs is whether they are tertiary amines which cross the blood-brain barrier (scopolamine, atropine, hyoscyamine) or quaternary amines, which do not (glycopyrrolate). Drugs which cross the blood-brain barrier are apt to cause CNS toxicity (sedation, delirium).

Drug	Trade Name	Route	Starting Dose	Onset
scopolamine (hyoscine) hydrobromide	Transderm Scop	Patch	One 1.5 mg patch	~12 h (24 h to steady state)
hyoscyamine	Levsin	PO, SL	0.125 mg	30 min
glycopyrrolate	Robinul	PO	1 mg	30 min
glycopyrrolate	Robinul	SubQ, IV	0.2 mg	1 min
Atropine sulfate	Atropine	SubQ, IV	0.1 mg	1 min
atropine sulfate	multiple	Sublingual	1gtt (1% ophth. soln)	30 min

Pharmacological pearls

- Glycopyrrolate has five times the anti-secretory potency compared to atropine but is poorly and erratically absorbed orally. The clinical significance of this is unclear.
- The scopolamine patch releases ~1 mg over 72 hours. It takes 24 hours to reach steady state and for acute symptoms other drugs should be used. The patch should be placed on hairless skin just behind the ear, is changed every 72 hours, and more than one patch can be used at a time.
- Hyoscyamine is available in short-acting, sustained-released, orally dispersible tablet, and oral solution formulations.

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FAST FACTS AND CONCEPTS #114
MYOCLONUS
Nicholas DeMonaco and Robert Arnold MD

Background Myoclonus is an abnormal movement described as a sudden, brief, shock-like, involuntary movement caused by active muscle contraction (positive myoclonus) or inhibition of ongoing muscle contraction (negative myoclonus). Myoclonus can have a distribution that is focal, multifocal, or generalized. This *Fast Fact* discusses its causes, evaluation, and therapy.

Characteristics and Differential Diagnosis Hiccups are an example of normal, physiological positive myoclonus, while asterixis is an example of negative myoclonus seen with metabolic encephalopathy. In nocturnal myoclonus or periodic leg movement disorder, there is activity in the flexor muscles of the legs and feet during light sleep. It can be seen in the setting of chronic nervous system diseases or in elderly patients with no other abnormalities. The brief, shock-like movements of myoclonus may be difficult to distinguish from other involuntary movements such as cramps, spasms, fasciculations, and dystonia. Fasciculations are brief involuntary muscle twitches that, unlike myoclonus, often do not result in movement across a joint. Dystonia is characterized as slow, repetitive, patterned, sustained movements (an example is writers cramp). An acute dystonic reaction is often caused by dopamine blocking medications including certain antipsychotics (haloperidol), antiemetics (metoclopramide), and calcium-channel blockers.

Causes The etiologies of myoclonus are numerous. Near the end of life, metabolic abnormalities and medication-induced myoclonus predominate. Metabolic causes include liver failure, renal failure, hyponatremia, and hypoglycemia. The medications and toxins associated with myoclonus include opioids, anticonvulsants (gabapentin, phenytoin, valproate, lamotrigine, and phenobarbital), tricyclic antidepressants and selective serotonin reuptake inhibitors, contrast dye, anesthetics, antibiotics (penicillins, cephalosporins, imipenem, and quinolones), cannabinoids and the chemotherapeutic agent ifosfamide. Opioid-induced myoclonus occurs commonly and is often misdiagnosed (See *Fast Facts* #57, 58). When myoclonus occurs due to toxins or medications, the jerks are usually multifocal or generalized, may be provoked by a stimulus or voluntary movement, and are often accompanied by encephalopathy. Other causes of myoclonus include focal CNS damage from tumors, stroke, and encephalitis, generalized CNS dysfunction such as encephalopathies (viral, metabolic, genetic, or neurodegenerative), seizure disorders, anoxic injury, and disorders affecting the spinal cord and peripheral nerves.

Treatment Myoclonus can disrupt sleep, make coordinated movements difficult, and be bothersome to patients or families. Treatment consists of correction of the underlying cause and symptomatic treatment of the myoclonus. If the offending agent is a non-essential medication, it should be discontinued. In the case of opioid-induced myoclonus, rotation to a different opioid may help. Benzodiazepines are the primary symptomatic treatment at end-of-life. While any benzodiazepine will work, clonazepam and lorazepam are commonly used. A continuous infusion of midazolam has also been suggested given the drug's compatibility with morphine and short half-life, allowing rapid dose titration. Sedation is likely when using benzodiazepines. If sedation is to be avoided, anticonvulsants such as levetiracetam (1,000-3,000 mg/day) and valproic acid (1200-2000 mg/day) may be helpful. The muscle relaxant dantrolene in doses of 50-100 mg/day has been reported as effective.

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FAST FACTS AND CONCEPTS #133
NON-ORAL HYDRATION IN PALLIATIVE CARE
Robin Fainsinger MD

Background At the center of the debate with regard to hydration in terminally ill patients is the desire to maintain comfort and avoid unnecessary/distressing procedures. There is no controversy that terminally ill patients should be encouraged to maintain adequate oral hydration for as long as possible. However there is debate and controversy around the use of parenteral hydration. This *Fast Fact* discusses medical decision-making about non-oral hydration in palliative care settings; *Fast Fact #134* discusses techniques of hydration.

Arguments Against Hydration

- Comatose patients do not experience symptom distress.
- Parenteral fluids may prolong dying.
- With less urine there is less need to void and use catheters.
- With less gastrointestinal fluid there can be less nausea and vomiting.
- With less respiratory tract secretions there can be less cough and pulmonary edema.
- Dehydration can help reduce distressing edema or ascites.
- Dehydration may be a “natural” anesthetic to ease the dying process.
- Parenteral hydration can be uncomfortable (e.g. needles/catheters) and limit patient mobility.

Arguments For Hydration

- Dehydration can lead to pre-renal azotemia, which in turn can lead to accumulation of drug metabolites (notably opioids), leading to delirium, myoclonus and seizures. Hydration can reverse these symptoms in some patients leading to improved comfort.
- There is no evidence that fluids prolong the dying process.
- Providing hydration can maintain the appearance of “doing something,” even though there may be no medical value, and thus ease family anxiety around the time of death.

Ethical/Legal Issues In the United States, the following ethical/legal standards exist:

- Competent patients or their surrogates can accept or refuse hydration based on relevant information.
- Non-oral hydration is considered a *medical intervention*, not *ordinary care*. As such, there is no legal or ethical imperative to provide it unless the benefits outweigh the burdens.

Recommendation There is published medical literature to support both the use of, and the withholding of, non-oral hydration in patients near death; thus, there is no consensus on the single best approach to care. A Cochrane review of 6 relevant studies showed that sedation and myoclonus were improved with hydration in adult palliative care patients; however, discomfort from fluid retention was significantly higher in the hydration group and survival seemed to be the same between the groups. Key issues to be considered when determining the role of non-oral hydration include the following:

- Expressed wishes of the patient or surrogate decision-maker regarding use of hydration.
- Patient-defined goals; the presence of a specific goal may direct the clinician to use hydration as a means to improve delirium and potentially delay death.
- Symptom burden: symptoms related to total body water excess may improve by withholding hydration, while delirium may lessen with hydration.
- Burden to the patient and caregivers of maintaining the non-oral route of hydration.
- Family distress concerning withholding hydration/nutrition.
- When in doubt, a time limited hydration trial is an appropriate recommendation.

Clinician Self-Reflection Finally, it is important to recognize that health care providers often have biases for or against non-oral hydration near the end-of- life. Self-reflection upon these biases is crucial to help patients and families make decisions that are based on the best interests and goals of the patient/family unit.

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FAST FACTS AND CONCEPTS #256

FEVER NEAR THE END OF LIFE

Mallory Strickland BS and Erica Stovsky MD

Introduction Clinically significant fever is defined as an increase in body temperature (generally $> 38.5^{\circ}\text{C}$) in conjunction with an elevation of the hypothalamic set point. Hyperthermia is an uncontrolled elevation in body temperature without a change in the thermoregulatory center. This *Fast Fact* reviews the key elements in assessment and treatment of fever in patients near the end-of-life.

Pathophysiology Fever is mediated by exogenous pyrogens (microbes or their products) and pyrogenic cytokines (i.e. IL-1, IL-6, IFN α , TNF) which induce the synthesis of prostaglandin E2 (PGE2). Centrally, PGE2 increases production of cAMP, which raises the hypothalamic set point to febrile levels. Peripherally, this induces myalgias and arthralgias. Pyrogens/pyrogenic cytokines are produced by infection, inflammation, trauma/tissue necrosis, and tumors. Drugs can induce fever through various metabolic and immune responses as well as by mimicking endogenous pyrogens, inflicting direct tissue damage and interfering with heat loss. Common drugs in palliative care settings which cause fever include antibiotics, anti-psychotics (neuroleptic malignant syndrome) and opioid withdrawal. Fever associated with brain injuries is common, perhaps due to direct hypothalamic injury.

Assessment The extent of evaluation will depend on the patient's condition and overall goals of care. When indicated, a thorough history and physical exam is needed, looking for a) signs of infection, b) in cancer patients, evidence of disease progression, and c) a medication review. A typical infection laboratory and radiographic workup can be pursued if it will affect management. Common etiologies and clinical findings are reviewed below.

- **Infection:** look for a history of exposure (e.g. influenza), normal barrier violation (e.g. aspiration, skin ulcer), and neutropenia (for instance, if receiving chemotherapy). Associated signs/symptoms include elevated WBC, chills, spiking temperatures, and if severe, hypotension, tachycardia, mental status changes and neutropenia. **Note:** Newborns, the elderly, patients with chronic hepatic or renal failure, the immunocompromised, and those taking glucocorticoids can have serious infections without a fever.
- **Neoplastic Fever:** a diagnosis of exclusion. It is uncommon in solid tumors, more common in lymphomas. It is less likely to manifest as chills, hypotension, tachycardia, and mental status changes; however elevated ESR and CRP are common. It tends to be responsive to NSAIDs.
- **Medication-Induced:** there is no predictable time of onset from medication initiation to fever presentation. It resolves when suspected drug is stopped.
- **DVT/PE:** thought to cause fever through inflammation. Fever is inconsistently associated with DVT/PE in the literature, however these are common events in the end-of-life population.

Treatment Benefits and burdens of all therapeutic options should be weighed in the context of the patient's overall clinical picture, including whether a fever is actually distressing to a dying patient. When deciding *if* to treat the fever, ask patients who can communicate if the fever is uncomfortable, and whether or not breaking the fever is more uncomfortable than the fever itself. Although empiric, there is no compelling reason to think that treatment of fever actually reduces suffering for dying, unresponsive patients. *Education and reassurance* for family and other caregivers is most important in those situations.

- **Non-pharmacological Interventions**
 - Cooling blankets, ice packs, sponging, and fans. While these can bring down body temperature, they are noisy, labor-intensive, and distract family and other caregivers from more meaningful interactions at the death-bed.
- **Pharmacologic Interventions**
 - Discontinue any non-essential drugs if drug-induced fever is suspected.
 - Antipyretics work by inhibiting production of PGE2. Acetaminophen 650-1000mg* PO/PR/IV q4-6 hours PRN (maximum dose 4 g/day*) is considered first line given its low side effect profile. NSAIDs (oral, IV, rectal, subcutaneous) are also effective. Naproxen 250mg* q12hrs is particularly effective in neoplastic fever, and possibly diagnostic when infection is ruled out. The order can state "PRN for symptomatic fever" to discourage focus on the temperature measurement alone.

- Antibiotic therapy has been shown to be inconsistently useful in alleviating fever symptoms in terminally ill patients. While evidence is unclear as to the utility of providing antibiotic therapy, discussions should address their use as a potential treatment that may or may not improve symptoms and prolong life/delay death; time-limited trials can be appropriate.
- Glucocorticoids (oral, IM, IV) are also purported to be effective, however most of the data supporting their use exist in the neurological and head injury literature.

*Discussed doses are for adults.

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FAST FACTS AND CONCEPTS #313

THIRST IN PALLIATIVE CARE

April Zehm MD, Jonathan Mullin MD, Haipeng Zhang DO

Background Thirst is a common source of distress in the seriously ill. This *Fast Fact* reviews thirst in patients with serious illness. See *Fast Fact* #182 on causes and treatment of dry mouth.

Physiology Thirst is the desire to drink fluids in response to a water deficit. Social customs, dry mouth, accompanying food intake, fluid availability, and palatability all serve as cues to drink. Seriously ill patients encountered by hospice and palliative care clinicians are at risk for thirst due to dehydration, electrolyte disturbances, hypotension, xerostomia, and immobility which can impede access to water. Patients with heart failure (HF), with end stage renal disease (ESRD), on mechanical ventilation, and taking certain medications (e.g. anti-hypertensives, tolvaptan, diuretics, or SSRIs) are also at increased risk. While opioids cause xerostomia, whether or not they cause thirst is controversial (1,2).

Thirst vs. Xerostomia Thirst is the desire to drink, while xerostomia is subjective or objective dry mouth. While xerostomia can contribute to thirst, not all patients with dry mouth experience thirst. Similarly, thirsty patients may not have xerostomia present. Research studies often use xerostomia as a surrogate for thirst, making it difficult to evaluate the prevalence and treatment efficacy for either symptom independently. It is important that clinicians evaluate for xerostomia or thirst as independent symptoms and determine if reversible causative factors are involved.

Measurement In clinical and research settings, thirst is self-reported and has high individual variability. There is no consensus on the best way to measure the frequency, intensity, quality and distress of thirst. Unidimensional severity scales and a 6-item Thirst Distress Scale have both been used (3).

Thirst in dying patients Around 80-90% of dying patients report significant thirst (4,5). Given its high prevalence, providers should routinely assess for thirst among dying patients who are able to report the symptom. The use of artificial or medically-assisted hydration to alleviate symptoms of dehydration amongst the terminally ill remains controversial. The concern that dehydration-related symptoms, including thirst, can cause discomfort is weighed against the concern that iatrogenic over-hydration can lead to pain and dyspnea from fluid retention. Studies of thirst in dying patients conclude there is little relationship between artificial hydration and thirst (5-8). Instead, daily oral care and sips of oral fluid administered for comfort can improve thirst (5-9) and should be routinely offered (see *Fast Fact* #133). Concerned family and friends may be distressed that their loved one is experiencing thirst at the end of life, which can prompt requests for artificial nutrition or hydration. While these requests should be considered on a case by case basis, reassurance that artificial hydration is unlikely to alleviate thirst and comes with significant risks should be provided.

Patients with ESRD Thirst and xerostomia are associated with higher inter-dialytic weight gain (IWG) which in turn increases cardiovascular morbidity and mortality (10,11). Increasing the frequency of dialysis from three times per week to daily is the only change to dialysis that has conclusively shown to reduce thirst scores, but this has obvious practical limitations (12). Angiotensin converting enzyme inhibitors have been associated with a reduction in thirst scores and IWG, but this benefit does not seem to last beyond six months (13-16). Frequent gum chewing and saliva substitutes used more than six times per day may alleviate thirst for at least several weeks after initiation (17-18).

Patients in the ICU Significant thirst has been reported in over 70% of critically ill patients (19). An “ICU bundle” of oral swab wipes, sterile ice-cold water sprays, and a lip moisturizer has been shown to decrease thirst intensity, thirst distress, and dry mouth in ICU patients (20).

Patients with HF Liberalization of fluid restrictions has been shown to decrease thirst in patients with chronic, stable HF and hospitalized patients with acute, decompensated HF (21-22). Importantly, these and multiple other studies did not show any change in mortality or readmission rates. In consultation with

a patient's cardiology team, liberalization of fluid restrictions should be considered in patients with HF and distressing thirst, along with addressing medications that are causing dry mouth (23).

Summary In patients reporting thirst, perform a clinical assessment to differentiate xerostomia and thirst and identify potentially reversible causes of either symptom. Available evidence suggests thirst is common in dying patients and is unlikely to be improved with artificial hydration especially in non-awake patients. Education, emotional support, oral care, and sips of fluid should be offered instead. Patients with ESRD, HF, and intubated ICU patients may have specific interventions which can improve thirst.

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