



Fast Facts Core Curriculum

Renal

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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 #134
NON-ORAL HYDRATION TECHNIQUES IN PALLIATIVE CARE**Robin Fainsinger MD**

Background The decision to use or withhold non-oral hydration near the end-of-life is complex ([see Fast Fact #133](#)). This Fast Fact reviews the technical aspects of providing non-oral hydration. [Fast Fact #190](#) discusses the related issue of parenteral nutrition in advanced cancer patients.

Nasogastric and Gastrostomy Tubes The use of enteral feeding tubes to provide nutrition is beyond the scope of this *Fast Fact* ([see Fast Facts #10, 84](#)). If already in place, enteral feeding tubes provide easy access for supplemental hydration. Placement of enteral tubes solely for hydration management in the last few weeks of life is generally not indicated, as other less burdensome methods of hydration can be provided (see below).

Intravenous Hydration This method includes hydration via peripheral or central catheters. For short-term use, especially as a time-limited trial, intravenous hydration is a reasonable step. However, both peripheral and central catheters are plagued with problems of site selection, placement, and maintenance; clot formation; local skin irritation; and local or systemic bacterial infections.

Hypodermoclysis (subcutaneous infusions) Hypodermoclysis offers a number of advantages compared to the intravenous route due to greater ease of site access, the possibility of temporary disconnection to facilitate patient mobility, and ease and suitability for home administration. Thrombocytopenia may be a relative contraindication. Solutions with electrolytes should be used (e.g. 0.9% sodium chloride), as non-electrolyte solutions (e.g. 5% dextrose) can draw fluid into the interstitial space. Continuous infusion rates up to 120 ml/hr have been reported; patients can tolerate boluses of up to 500 ml/hr two to three times per day. Traditionally the use of hyaluronidase to promote absorption was recommended. More recent experience has demonstrated that most patients will achieve good absorption of subcutaneous fluids without hyaluronidase. Winged infusion sets with 25 – 27 gauge needles are recommended.

The upper chest is the commonly used site for hypodermoclysis. Utilization of the lower abdomen and upper thigh as sites for hypodermoclysis can be associated with scrotal edema in males. Most experts recommend avoiding the upper arm as a site for hypodermoclysis. Check the site frequently for redness, irritation, excessive edema, or a dislodged needle. If there is a problem with absorption it is recommended to a) slow the infusion rate and consider using an infusion pump, or b) consider dividing the total volume into two separate subcutaneous sites.

Rectal Hydration (proctoclysis) Rectal hydration is an alternative only when other resources are not available. A 22 French nasogastric catheter can be inserted approximately 40 cm into the rectum. The patient can be positioned as for any rectal procedure. Tap water can be used, and the rectal infusion increased from 100 ml to a maximum of 400 ml per hour, unless fluid leakage occurs before the maximum volume is achieved. The majority of patients can successfully tolerate this approach at a volume of 100 to 200 ml per hour.

Fluid Volumes For all routes, a reasonable goal is 1-1.5 L/day in fluid volume.

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FAST FACTS AND CONCEPTS #161 OPIOID USE IN RENAL FAILURE

Robert Arnold MD, Peg Verrico RPh, Sara N Davison MD

Background Chronic pain is common in chronic kidney disease impacting 50% of hemodialysis patients, 82% of whom experience moderate to severe pain. The absorption, metabolism, and renal clearance of opioids are complex in renal failure. However, with the appropriate selection and titration of opioids, patients with renal failure can achieve analgesia with minimal risk of adverse effects. This *Fast Fact* reviews recommendations for opioid use in the setting of renal failure and in patients receiving chronic dialysis.

Not Recommended for Use:

- **Meperidine** is not recommended in renal failure due to accumulation of normeperidine, which may cause seizures.
- **Codeine** has been reported to cause profound toxicity which can be delayed and may occur after trivial doses. We recommend that codeine be avoided in patients with a Glomerular Filtration Rate (GFR) <30 mL/min.
- **Dextropropoxyphene** is associated with central nervous system (CNS) and cardiac toxicity and is not recommended for use in patients with renal failure.
- **Morphine** is not recommended for chronic use in renal insufficiency (GFR <30 mL/min) due to the rapid accumulation of active, nondialyzable metabolites that are neurotoxic. If morphine must be used, avoid long-acting preparations and monitor closely for toxicity (see *Fast Facts* #57, 58).

Use with Caution:

- **Oxycodone** is metabolized in the liver with 19% excreted unchanged in the urine. There are reports of accumulation of both the parent compound and metabolites in renal failure resulting in CNS toxicity and sedation.
- **Hydromorphone**, as the parent drug, does not substantially accumulate in hemodialysis patients. Conversely, an active metabolite, hydromorphone-3-glucuronide, quickly accumulates between dialysis treatments but appears to be effectively removed during hemodialysis. With careful monitoring, hydromorphone may be used safely in dialysis patients. However, it should be used with caution in patients with a GFR < 30mL/min who have yet to start dialysis or who have withdrawn from dialysis.

Safest in Renal Insufficiency:

- **Fentanyl** is considered relatively safe in renal failure as it has no active metabolites. However, very little pharmacokinetic data exist regarding fentanyl in end stage renal disease. While some studies have shown decreased clearance in renal failure, most studies do not show drug accumulation. Fentanyl is not dialyzable due to high protein binding and a high volume of distribution.
- **Methadone** is considered relatively safe in renal failure. It has no active metabolites and limited plasma accumulation in renal failure due to enhanced elimination in the feces. However, precautions regarding the use of methadone exist (See *Fast Facts* # 75, 86). It does not appear to be removed by dialysis.

Opioid Dosing Given the lack of pharmacokinetic and pharmacodynamic data of opioids in renal failure, it is difficult to advocate for specific analgesic treatment algorithms. However, the following guide has been proposed (Broadbent 2003) for the *initial* dosing of the safer opioids in renal impairment and renal failure.

- Creatinine Clearance > 50 mL/min: normal dosing.
- Creatinine Clearance of 10-50 mL/min: 75% of normal.
- Creatinine Clearance < 10 mL/min: 50% of normal.

The “normal opioid dose” for any given patient is the dose that adequately relieves pain without unacceptable adverse effects (see *Fast Fact* #20). Rarely, do opioids need to be adjusted when GFR is > 50 mL/min. While opioids can be used when GFR is <50, they require closer monitoring and constant reassessment to ensure that accumulation of active metabolites does not result in toxicity. This should not preclude the effective use of opioids in these patients.

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FAST FACT AND CONCEPT #163
DECISION MAKING IN CHRONIC KIDNEY DISEASE (CKD)
Sara N Davison, MD

Background Care of patients with CKD requires expertise in advance care planning (ACP), including attention to ethical, psychosocial, and spiritual issues related to starting, continuing, withholding, and stopping dialysis. This *Fast Fact* reviews key concepts of the ACP process for CKD patients.

Barriers to ACP in CKD

- **Being unaware of a poor prognosis.** CKD patients may falsely assume they can be kept alive indefinitely on dialysis; end-of-life issues are commonly avoided until late in the illness.
- **Many health professionals believe that ACP may destroy hope** and that the focus of care should be on their “life-sustaining therapy”, i.e. dialysis.
- **Cognitive dysfunction** associated with advanced CKD may prevent the ability for meaningful participation in ACP. Discussions must occur early in the illness while comprehension and decision-making capacity are preserved.

Key Aspects of ACP in CKD (See *FF* #162 for general ACP recommendations)

- **ACP should be initiated prior to the need for dialysis.** The importance of early discussions is underscored by the fact that only ~ 60% of nephrologists would consider stopping dialysis for a non-decisional patient with unclear prior wishes.
- **Include family in ACP discussions.**
 - **CKD patients are often afraid to talk to their loved ones** about their preferences; some patients will choose to prolong their time on dialysis due to family pressure.
 - **Surrogates must be aware of patient preferences** and the values upon which these preferences were based.
 - **Including family is critical in achieving many of the goals of ACP** such as strengthening relationships with and relieving emotional and financial burdens on loved ones.
- **Provide detailed information as part of pre-dialysis education.**
 - **All treatment options should be fully reviewed:** 1) available dialysis modalities, 2) not starting dialysis and continuing conservative management, 3) a time-limited trial of dialysis, and 4) stopping dialysis with expectation of death. (See below for clinical practice guidelines on not starting or discontinuing dialysis).
 - **Estimate prognosis.** The annual death rate for patients initiating dialysis is 20-25%; 15% - 25% of these deaths result from decisions to withdraw dialysis. Patients with CKD who elect dialysis generally experience progressive functional decline over months to years, punctuated by episodes of life-threatening complications. Elderly or chronically ill patients with co-morbid diseases, at the initiation of dialysis, can be expected to have greater complications and a shorter survival. Poor prognostic factors include older age, low serum albumin, poor functional status, and comorbid illnesses such as diabetes and cardiovascular disease. Anuric patients, who elect to not initiate or discontinue dialysis, typically survive for 7-14 days. The prognosis is longer for patients with residual renal function who continue to make urine.
 - **Emphasize how you expect their illness and proposed treatments will impact their daily function.** Discuss the impact of the various dialysis options on day-to-day function.

Patients Selection for Withholding or the Withdrawal Dialysis (1)

1. Patients who, being fully informed and making voluntary choices, decline to begin or request dialysis be stopped.
2. Patients who no longer possess decision-making capacity, who have previously indicated refusal of dialysis.
3. Patients who do not possess decision-making capacity and whose surrogate declines dialysis or determines it should be discontinued.
4. Patients with irreversible, profound neurological impairment such that they lack signs of thought, sensation, purposeful behavior, and awareness of self and environment.
5. Patients whose medical conditions precludes the technical process of dialysis.

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**FAST FACTS AND CONCEPTS #191
PROGNOSTICATION IN PATIENTS RECEIVING DIALYSIS**

Matthew Hudson, Steven Weisbord MD, Robert Arnold MD

Background End stage renal disease (ESRD) is a highly prevalent and rapidly increasing condition. While dialysis prolongs life in patients with ESRD, life expectancy remains only a third to a sixth as long as similar patients not on dialysis. The overall one and five year mortality rates are 25% and 60%, respectively. Approximately 20% of ESRD patient deaths occur after a decision to stop dialysis, highlighting the importance of discussions of prognosis and goals of care with this chronically ill population. This *Fast Fact* reviews the current data regarding prognostication in patients receiving chronic hemo- and peritoneal dialysis. **Note:** renal transplantation reduces mortality and the following data do not consider patients with functioning kidney transplants.

Prognostic Factors Several patient-specific factors influence prognosis:

- **Age:** For 1-year increments beginning at age 18, there is a 3 to 4% increase in annual mortality compared to the general population. 1 and 2 year mortality rates go from 10 and 12% at 25-29 years of age, to 25% and 42% at 65-69 years, to 39% and 61% at 80-84 years of age.
- **Functional status:** the relative risk of dying within 3 years of starting dialysis is 1.44 for those with Karnofsky Performance Status scores of <70 compared to a score ³70 (see *Fast Fact* #13).
- **Albumin:** a low serum albumin level, both at baseline and during the course of dialysis treatment, is a consistent and strong predictor of death. For example, the 1 and 2 year survival of patients with an albumin of >3.5 g/dL is 86% and 76% respectively, compared to 50% and 17% if less than 3.5.
- **Surprise question:** in a multivariate analysis, the likelihood of death in 6 months was significantly greater when nephrologists answered no to the question “*would I be surprised if this patient died within 6 months?*”

Prognostic Tools It has long been recognized that patient comorbidity is strongly correlated with prognosis in ESRD. An age-modified Charlson Comorbidity Index (CCI), which stratifies patients based on medical comorbidities and age, has been successfully used to predict mortality in dialysis-dependent patients (8):

Modified Charlson Comorbidity Index: Total score is the sum of the comorbidity points

Comorbidity Points				
1 point each for coronary artery disease, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disorder, peptic ulcer disease, mild liver disease, diabetes 1 point for every decade over 40 (e.g. a 65 year old would receive 3 points).				
2 points each for hemiplegia, moderate-to-severe renal disease (including being on dialysis), diabetes with end-organ damage, cancer (including leukemia or lymphoma)				
3 points for moderate-to-severe liver disease				
6 points each for metastatic solid tumor or AIDS				
Modified CCI Score Totals	Low score (≤3)	Moderate (4-5)	High (6-7)	Very High (≥8)
Annual mortality rate	0.03	0.13	0.27	0.49

For example, a 66 year old male on dialysis with a history of CHF, COPD, and diabetes with retinopathy would have a CCI score of 9 and a nearly 50% chance of dying within a year. Using this, a provider could discuss with the patient his prognosis and use this to facilitate further discussion regarding planning for the future, including end-of-life decisions. The Index of Coexistent Disease (ICED), a general illness severity index, has also shown predictive power in ESRD. The scale's complexity and length however (it entails asking over 100 questions) limit its clinical usefulness.

Summary The age-modified CCI, in conjunction with other prognostic factors such as serum albumin and functional status, can be used to help facilitate discussions with dialysis-dependent patients and their families regarding goals of care and end-of-life planning.

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**FAST FACTS AND CONCEPTS #207
WITHDRAWAL OF DIALYSIS: DECISION-MAKING**

Sara N Davison MD and Drew A Rosielle MD

Background Historically, stopping dialysis was considered by many to be a form of suicide. Now, it is a widely accepted practice in most countries, with broad ethical and legal consensus that dialysis can be stopped when it is no longer achieving a meaningful goal for the patient. In fact, ~25% of deaths of dialysis patients in North America occur after its cessation. This *Fast Fact* reviews key issues pertaining to the decision to stop chronic dialysis; *Fast Fact* #208 will discuss the care of patients after it is stopped.

Why dialysis is stopped The goal of dialysis is not only to prolong life by providing renal replacement therapy, but to maintain a patient's quality of life at an acceptable level (see *Fast Fact* #163). Discussions to stop dialysis usually occur when:

- Dialysis is no longer serving to substantially prolong life or is only prolonging a patient's death (e.g., a patient dying from advanced cancer or sepsis with multiorgan system failure).
- The burdens of dialysis and its complications outweigh its life-prolonging benefits to a patient (e.g., a patient with progressive frailty who is becoming bedbound; a patient with severe cognitive failure). In these scenarios dialysis is likely to prolong life but is not helping to restore a patient to an acceptable level of quality of life as assessed by the patient or her/his surrogate decision maker.

Demographics The demographics of dialysis withdrawal have been studied at length. Patient characteristics associated with withdrawal are older age, female, white race, longer duration of dialysis, higher educational level, living alone, severe pain, and comorbidity (with chronic or progressive diseases). Ethnic differences have been observed, with African Americans and Hispanics being less likely to stop dialysis than European Americans. Reported prevalence levels of patient decision-making capacity at the time of withdrawal vary considerably with estimates ranging from 37% to 80%, suggesting cognitive failure drives many of these decisions. Nephrologists rate cognitive and physical functional status as the most important factors for their decision-making around stopping dialysis, and 93% of North American nephrologists report a willingness to honor a patient's request to stop, even if they have a personal preference to continue. Internationally, practices vary tremendously, with much lower rates of dialysis cessation in Japan compared to North America, for instance.

Responding to a request to stop dialysis For patients who are otherwise dying, counsel about terminal care issues surrounding dialysis withdrawal (see *Fast Fact* #208). For patients not otherwise close to death, explore reasons for withdrawal, especially for treatable factors that might contribute to the desire to withdraw dialysis. For patients whose desire to stop dialysis is being driven by factors that are potentially ameliorable, clinicians should make sure that the decision to stop dialysis is fully informed, including the possibility that some concerns could be addressed. These include:

- Inadequately treated depression, anxiety, pain, and other physical or psychological symptoms (including spiritual and existential suffering)
- Dissatisfaction or difficulties with dialysis itself (e.g., modality, time commitment, or treatment setting)
- Inadequate social support, or concerns with being a burden to loved ones.

Offer to evaluate and treat these concerns; consider a time-limited trial to see if a patient's quality of life can be improved. However, once a clinician feels a patient or surrogate is making a fully informed choice that is consistent with a patient's values and goals, that decision should be honored. Proactively address any concerns patients may voice about the ethics of withdrawal.

Broaching dialysis withdrawal Clinicians who are concerned continuing dialysis is no longer benefitting a patient due to the reasons described above should broach discontinuation with the patient and family. This discussion should occur as part of a larger goals-of-care conversation which addresses prognosis (see *Fast Fact #191*), patient/family assessment of quality of life, and establishes realistic care goals. Dialysis should be discussed as part of an overall medical plan and framed as how it can or cannot address the care goals. *“Dialysis will likely make your mother live longer. However – given everything that has been happening – it is not going to improve her strength, memory, or ability to take care of herself. Based on what you’ve told me about your mother and what is important for her, I would recommend stopping the dialysis as it is only serving to maintain her in a state she would find unacceptable.”*

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**FAST FACTS AND CONCEPTS #208
CLINICAL CARE FOLLOWING WITHDRAWAL OF DIALYSIS**

Sara N Davison MD and Drew A Rosielle MD

Background *Fast Fact #207* discussed decision-making around dialysis discontinuation; this *Fast Fact* addresses care of the patient around the time of discontinuation.

Communication and care-planning at the time of dialysis cessation

- Counsel about what to expect: mean survival following dialysis withdrawal is 8-10 days (although rarely can be many weeks). Address the likelihood of progressive encephalopathy.
- Reassure patients/families that symptoms can be adequately treated (see below), although drugs with sedating side effects may be necessary to ensure comfort.
- Discuss diet: a liberal, pleasure-based diet is appropriate for many patients although they should be cautioned it could worsen symptoms from edema.
- Address potential care sites for the final days of life.
- Review other medical treatments the patient is receiving and discontinue those that will not improve their quality of life while dying; clarify treatment limitations including resuscitation (code) status.
- Provide emotional/psychological, spiritual, social work, and bereavement support services.

Symptom Management In one cohort of hospitalized patients who stopped dialysis confusion/agitation was reported to affect 70% of patients, followed by pain (55%), dyspnea (48%), nausea (36%), twitching/seizures (27%), anxiety/psychological distress (27%), pruritis (24%), and peripheral edema (21%). Because of a paucity of clinical research, the following recommendations are largely based on clinical experience and pharmacologic common sense. Many drugs which were previously cleared by dialysis may need to be dose-adjusted or discontinued. Treatment plans should be frequently re-evaluated, with particular attention to the use of scheduled medications.

- **Pain management:** Acetaminophen is the agent of choice for mild pain. *Fast Fact #161* addresses opioid use in renal failure. Fentanyl and methadone are considered safest after dialysis discontinuation, although methadone should only be initiated by clinicians familiar with its use. Toxic hydromorphone metabolites, previously cleared by dialysis, can accumulate rapidly once dialysis is stopped and it should be used with caution and close monitoring of side effects. Gabapentin and pregabalin quickly accumulate once dialysis is stopped and should be discontinued or severely dose-reduced (see *Fast Fact #49*).
- **Shortness of breath:** Oxygen, positioning, and opioids are the mainstays of therapy (see *Fast Fact #27*). Ultrafiltration is not recommended as it can be distressing for patients/family to see the patient back on a therapy which appears similar to hemodialysis. For the occasional patient who has a residual urine output of >100 ml/day, high dose diuretics can be used.
- **Anxiety/agitation/restlessness:** Assure pain and psychosocial issues are addressed. Haloperidol or benzodiazepines are effective. Haloperidol may lower the seizure threshold and the metabolites are excreted in the urine and feces so it is recommended to dose at half the typical starting dose following dialysis withdrawal. While benzodiazepines do not accumulate in chronic kidney disease, clinical experience supports starting with low doses.
- **Restless legs:** Clonazepam is particularly useful for the restless legs associated with uremia (0.5 – 2.0 mg bid). Clonidine (0.1-0.2 mg bid) can also be used.
- **Muscle cramps:** Dialysis patients are often treated with quinine sulphate which accumulates rapidly once dialysis is stopped and should be discontinued. Clonazepam and other benzodiazepines are better in this setting.
- **Nausea:** Reduced doses of metoclopramide (starting at 5 mg bid) are effective for gastroparesis. Uremia-induced nausea often responds well to dopamine antagonists such as haloperidol and prochlorperazine which are often sedating in the context of uremia. Ondansetron has some advantages as it is less sedating and does not accumulate in kidney failure.
- **Pruritus:** Emollients such as hydrourea cream, ondansetron, and antihistamines may be beneficial. Gabapentin, while effective, is too toxic in this population to initiate its use.
- **Myoclonus:** See *Fast Facts #114*. Often it emerges from uremic encephalopathy and is mild in nature (e.g. 1-3 jerks per minute involving hands or feet). However, myoclonus can be distressful and wake patients from sleep. Empiric use of clonazepam or other benzodiazepines is the mainstay of treatment.

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FAST FACTS AND CONCEPTS #220 HYPODERMOCLYSIS

Arif H Kamal MD and Eduardo Bruera MD

Background This *Fast Fact* discusses subcutaneous fluid infusions, also known as hypodermoclysis (HDC). The use of parenteral hydration in dying patients is controversial and is discussed in *Fast Fact* #133. While this *Fast Fact* discusses subcutaneous fluid infusions for purposes of hydration, similar techniques can also be used to deliver medications (see *Fast Fact* #28).

Historical and Current Practice Hypodermoclysis was a widely accepted route for parenteral hydration in the 1940s and 1950s before falling out of favor after several reports of adverse reactions, likely related to the use of hypertonic and electrolyte-free solutions. Due to its ease of use, and subsequent research demonstrating its safety and efficacy, HDC has become more widely used. In the US, HDC is mostly used in geriatric and palliative care settings, although it is used more widely elsewhere in the world.

HDC vs. Intravenous Hydration Decisions for parenteral hydration in dying patients are complex and individual decision making is paramount. When parenteral hydration is indicated, clinicians are generally faced with a decision to use HDC or intravenous (IV) hydration (see *Fast Fact* #134).

- **Advantages of HDC over IV:** Starting and maintaining a subcutaneous infusion catheter is relatively pain-free. It can be done by trained patients or family caregivers, preventing the need for frequent skilled nursing visits or trips to medical centers to maintain a working IV. HDC provides greater potential sites for needle placement (arm, back, abdomen, thighs), and equipment costs are generally lower than with IVs. Subcutaneous catheters can be easily disconnected from IV tubing and re-used later, allowing a patient to receive intermittent fluid treatments. Portable infusion devices are not needed with HDC. HDC infusions may also cause less agitation in patients with dementia versus IV (1).
- **Disadvantages:** HDC is limited by a continuous infusion rate of 1-2 ml/min or 1.5-3 L/day (2). This is adequate for most clinical situations, and additional catheters can be added if needed. Bolus infusions (up to 500 ml/hour) are possible with HDC, but often require hyaluronidase (see below). Both HDC and IV infusions have similar rates of local adverse events (e.g. erythema, cellulitis) and lifespan of infusion site (3). HDC can be technically difficult in patients with substantial peripheral edema, as well as in cachectic patients with little subcutaneous tissue. Patients and families may have pre-conceived attitudes about greater benefits with IV routes even while acknowledging increased burden (4).

Technique

- **Equipment needed:** Small butterfly needle (usually 22 gauge) or angiocatheter, skin preparation (alcohol or iodine), sterile occlusive dressing, solution bag (saline or saline-dextrose combination), tubing with drip chamber. The use of an electrolyte free solution like 5% dextrose is discouraged due to third-spacing risks which can cause tissue sloughing or rarely circulatory collapse.
- **Procedure:** After cleaning the local site, insert the needle bevel up into the subcutaneous tissue. Attach to fluid and tubing and cover with occlusive dressing. Select an infusion fluid and set drip rate or fluid bolus. Normal saline (NS) is typically used although half-normal saline or 2/3 D5W in 1/3 NS have been used in clinical practice. Drip rates can be set to 20-125 ml/hour with gravity (no pump required) or 1-2 ml/minute. Some patients may prefer drips set to gravity 24 hours per day at a low rate (e.g. 50 ml/hour), overnight hydration (e.g. 100 ml/hour), or intermittent fluid boluses (e.g. 500 ml). The volume of infusion needed to keep acceptable levels of hydration in many palliative care patients is lower than healthy patients and postulated to be ~1 L/day (5). No evidence exists for the

frequency of site change. Some change only when there are symptoms or needle displacement while others choose a fixed time (e.g. every 3 or 7 days) or fluid volume (e.g. every 1.5 L). Teflon cannulas, although expensive, can be used for a week and are helpful for patients who have trouble maintaining a catheter site (6). Local anesthetic creams may be helpful during catheter placement to reduce discomfort, especially in children.

- **Recombinant human hyaluronidase:** RHH is an enzyme that temporarily lyses the subcutaneous interstitial space to promote diffusion of fluid. It can be used for site discomfort or if a faster rate of absorption is desired. Previous preparations were of bovine origin and were associated with local allergic reactions, anaphylaxis, and pain, making its role controversial. RHH has shown no human allergenicity (7). Recent studies have investigated RHH versus placebo in a randomized trial with gravity-driven infusion. The RHH group showed higher obtainable fluid rates, decreased discomfort, and similar local reactions. Doses of 150 U to 750 U given as steady push prior to the infusion can yield fluid rates of 380 to 520 ml/hour (8).

Cautions Uncommon local reactions include edema, local pain, or erythema. Interventions include slowing the rate, changing the site, or using RHH. Rare complications include cellulitis and vascular puncture. Systemic complications such as pulmonary edema can occur with all types of artificial hydration.

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FAST FACTS AND CONCEPTS #287 DRUG-INDUCED ACUTE URINARY RETENTION

Winifred Teuteberg MD

Background Acute urinary retention (AUR) is defined as a sudden inability to urinate, which is usually painful and requires catheterization (1). This can impair quality of life, and can cause kidney injury (2). A variety of medications used for symptom management can contribute to urinary retention. This *Fast Fact* will review medication-induced AUR and offer management strategies.

Clinical features and evaluation Signs and symptoms of AUR include bladder/suprapubic pain and tenderness and new onset overflow incontinence. The presence of AUR should be assessed in older patients who develop delirium, particularly if they have underlying dementia. Medications are a common cause of AUR. Common non-drug etiologies include benign prostatic hypertrophy, malignancy (e.g., epidural spinal cord compression), neurogenic bladder, and fecal impaction. There are little data on the incidence of AUR in palliative care. However, a small observational study showed that 15% of patients admitted to a large palliative care program had urinary retention (3). In contrast to AUR, chronic urinary retention is difficult to define as urine volumes vary greatly between patients. Chronic urinary retention is often the result of chronic neurologic condition or benign prostatic hypertrophy. A key difference between acute and chronic urinary retention is that chronic urinary retention is often asymptomatic and rarely painful due to gradual distention of the bladder over time. Common symptoms of chronic urinary retention include frequency, hesitancy and decreased force of urine stream (4).

Medications Associated with AUR Medications with anticholinergic properties (e.g., antipsychotics antihistamines and many anti-emetics and antidepressants) as well as opioids and anesthetics are commonly associated with AUR. Other drugs include alpha-agonists, benzodiazepines, NSAIDs, detrusor relaxants (e.g., oxybutynin), and calcium channel antagonists. Elderly patients are more at risk due to increased prevalence of benign prostatic hypertrophy (BPH) and polypharmacy.

- Selective serotonin reuptake inhibitors (SSRI's) are an under-recognized cause of retention. One prospective study found that urinary retention occurred in about 10% of patients prescribed SSRI's and the symptom often leads to the discontinuation of the medication (5).
- Opioids causing urinary retention has long been recognized, and is most studied in post-operative adult patients where its incidence is approximately 25% (6). All opioids can cause urinary retention due to mu-opioid receptor agonism.

Post Void Residual is the volume of urine left in the bladder at the end of micturition. The gold standard for PVR measurement is a transurethral catheterization; however due to the discomfort involved, non-invasive bladder volume estimation via a portable bladder scanner is a commonly utilized alternative often performed by the bedside nurse. Threshold values delineating what constitutes an abnormal PVR are poorly understood and PVR measurements utilizing portable scanners can be inaccurate in the presence of ascites (7). In general, clinical management decisions should be based on the patient's symptoms and the trends in the PVR measurements rather than a strict threshold PVR measurement. For example, an acute increase in PVR values from 200 mL to 450 mL in the setting of acute onset suprapubic pain or discomfort is indicative of AUR, whereas an asymptomatic patient with a PVR of 300 mL may not need any intervention at all.

Physical Exam A distended bladder is palpable as a tender suprapubic mass once it has reached a urine volume of 150 mL. Bladders with volumes in excess of 500 mL can manifest as a visible suprapubic mass in thin patients. Because a normal bladder volume is less than 50 mL, AUR can be missed on physical exam, particularly in obese patients.

Clinical Management AUR can be a medical emergency; hence, such patients should be catheterized to relieve bladder distension. Depending on the age of the patient, patients should be treated with either in-and-out catheterization followed by a trial of spontaneous voiding or be sent home with an indwelling bladder catheter for several days to a week. Patients older than 75 years and those with PVRs greater than 1000 mL are less likely to have successful voiding after a one-time catheterization. Medications should be reviewed and offending agents should be stopped or dose-limited. If BPH is a contributing factor, the addition of BPH drugs, such as 5- α reductase inhibitors and α -antagonists, can help improve urine flow (6). If a spontaneous voiding trial fails after adjustment of medication and several days of catheterization, a referral to urology is warranted (8).

For patients with a limited life expectancy for whom causative medications cannot be adjusted, life-long indwelling catheterization or intermittent catheterization are reasonable options. Although many clinicians may consider catheterization to be burdensome, a survey of patients with neurogenic bladders using long-term indwelling or intermittent self-catheterization found that the majority of patients felt that the use of catheterization positively impacted quality of life (9).

Novel Pharmacologic Management Strategies If the offending pharmacotherapy cannot be stopped, targeted pharmacotherapies may be able to counteract urinary retention, although such use is considered investigational. Opioid antagonists such as naloxone and methylnaltrexone can block opioid receptors and allow for normal urination per a case report and a single, pre-clinical controlled trial (10,11). One case report described the reversal of citalopram-related AUR by the addition of mirtazapine (12).

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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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**FAST FACTS AND CONCEPTS #325
UREMIC CALCIPHYLAXIS**

Katherine Roza MD, Jason C. George DO, Maria Bermudez MD and Zankhana Mehta MD.

Calciphylaxis is a poorly understood disorder in which calcification of small blood vessels causes painful ischemic skin and visceral lesions most often in patients with end-stage renal disease (ESRD). This *Fast Fact* will review its clinical presentation and offer recommendations for advance care planning and symptom management.

Epidemiology: Calciphylaxis occurs in 4% of ESRD patients on peritoneal dialysis or hemodialysis and can occasionally occur in pre-dialysis renal disease (1). Risk factors include: female sex; Caucasian race; obesity; diabetes mellitus; hyperparathyroidism; albumin < 3; hypercoagulable states; and exposure to certain medications such as warfarin, iron, vitamin D, and corticosteroids (2-7).

Pathophysiology: Uremia, calcium products, and reactive oxygen species (ROS) associated with ESRD are thought to increase vascular calcium deposition and fibrosis, leading to calciphylaxis (1,3). Over time this process likely precipitates arteriolar remodeling and progressive stenosis, causing ischemia and skin infarcts. The one-year mortality rate for calciphylaxis is estimated to be 45-80%, which may be even higher when ulcerative skin lesions are present (7,8). Ischemic complications and difficult to treat infections given incomplete antibiotic penetrance and poorly perfused tissues are potential mechanisms for the increased mortality risk.

Clinical Presentation: Early signs include pain and a lace-like purplish discoloration of the skin (livedo reticularis). This is often followed by painful subcutaneous nodules or plaques that progress to necrotic ulcerations. Areas of greatest fat tissue -- abdomen, buttocks, and inner thighs -- are most commonly involved, although visceral organs, skeletal muscle, and heart muscle can also be affected (5, 9). Calciphylaxis can be challenging to distinguish from a vasculitis. Intact pulses, bilateral upper extremity involvement, and calcification seen on X-rays or CT scans are suggestive indicators of calciphylaxis.

Diagnosis: Calciphylaxis is a clinical diagnosis. Laboratory findings are non-specific. In certain circumstances, a dermatology consult and/or skin biopsy may be needed. However, skin biopsy is usually deferred due to risk of pain, a false negative result, and poor wound healing (2,10). Imaging studies can support the diagnosis by identifying calcification, but they do not confirm a diagnosis and may lead to unnecessary discomfort (10).

Treatment: No randomized control trials exist for the treatment of calciphylaxis. In general, most experts recommend a multi-modal approach involving adequate wound care, pain control, and treatment of hyperparathyroidism. This includes a low phosphate diet, use of non-calcium based phosphate binders (i.e., sevelamer), and cessation of vitamin D supplementation. In hemodialysis patients, calcimimetics (i.e. cinacalcet) and increasing dialysis frequency to 4 to 6 sessions per week may help but evidence is limited to case reports (3,11). Other less established options include sodium thiosulfate infusion during hemodialysis, oxygen therapy (10-15 liters via face mask 2 hours/day), and hyperbaric oxygen directed to the wound (3,5,12,13). Providing these therapies may be logistically challenging for hospice agencies.

Pain Management: The mechanism of pain is poorly understood, but is thought to be due to ischemia and resultant nerve damage. No controlled studies have confirmed an optimal analgesic approach. However, case series suggest that combining aggressive wound care with an analgesia regimen consisting of opioids, ketamine, and non-opioid adjuvants (e.g., gabapentin or tricyclic antidepressants) can be effective (14). Fentanyl, buprenorphine and methadone do not have known renal metabolites and thus may be associated with less opioid toxicity. The use of topical ketamine or topical opioids, such as morphine-infused gels may offer local pain control with potentially less systemic side effects, but this has not yet been studied (see *Fast Facts* # 185). Amputation remains an option in cases of refractory pain.

Advance Care Planning: Considering the one-year mortality risk, the diagnosis of calciphylaxis should prompt clinicians to engage patients and families in a larger discussion regarding advance directives, prognosis, and goals of care. A potential decision-point is whether to withhold or withdraw hemodialysis when calciphylaxis is diagnosed. Patients may not be aware that stopping dialysis is a viable care option unless raised by a clinician. Clinicians, however, should be aware

that the decision to stop hemodialysis can be exceedingly complex and dependent upon a variety of factors such as patient-defined quality of life, symptom burden, prognosis, and care location preferences (see *Fast Fact* #163). While the Medicare Hospice Benefit (MHB) can provide important care resources and support for patients with calciphylaxis, MHB patients are typically unable to continue dialysis with a hospice admitting diagnosis of ESRD. Thus, even a discussion of hospice can be challenging to navigate for many clinicians. Given their skills in managing complex analgesic regimens and their multidisciplinary approach to clinical, psychological, spiritual, and social care, the involvement of a specialist palliative care team can be helpful when discussing withholding or withdrawing dialysis.

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FAST FACTS AND CONCEPTS #337
PALLIATION OF BLADDER SPASMS
Elise De MD, Pablo Gomery MD, and Leah B. Rosenberg MD

Background: Bladder spasms induced by involuntary bladder contractions are a distressing symptom affecting 7-27% of men and 9-43% of women (1). Seriously ill patients may develop bladder spasms as a complication from genitourinary malignancies, indwelling catheters, or other medical issues. For some, these contractions may be imperceptible and only appreciated on urodynamic testing; for others, they can be incapacitating and associated with urinary incontinence.

Differential Diagnosis: Common etiologies of bladder spasms include a urinary tract infection (UTI), ingestion of chemical irritants like diet soda or caffeine, constipation, obstruction of the bladder outflow tract (e.g. non-emptying catheter from blood clots), disinhibition from interruption of upper motor neurons, or irritation of the detrusor muscle from a tumor, catheter, or intramural stone (2). Medications can also lead to spasms either by bladder irritation (e.g. diuretics) or disruption of the detrusor muscle or bladder outlet (e.g. opioids, anticholinergics,