

 **PALLIATIVE CARE
NETWORK OF WISCONSIN**
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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Authors' Affiliations: Geisinger Medical Center, Danville, Pennsylvania.

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