# Calciphylaxis and Kidney Disease: A Review

SHAHAB MOGHADAM

# Calciphylaxis and Kidney Disease: A Review

- **Calciphylaxis is a life-threatening complication most often associated with chronic kidney disease that occurs as a result of the deposition of calcium in dermal and adipose microvasculature.**

- **this condition may also be seen in patients with acute kidney injury.**

# Calciphylaxis and Kidney Disease: A Review

**.we review the literature on uremic calciphylaxis with a focus on its pathophysiology, clinical presentation, advances in diagnostic tools, and treatment strategies.**

**. This review emphasizes the need for multidisciplinary collaboration including nephrology, dermatology, and palliative care to ultimately provide the best possible care to patients with calciphylaxis.**

# Clinical Vignette

**.middle-aged man with cirrhosis secondary to alcohol related liver disease was admitted for sepsis in the setting of pneumonia. His clinical course was complicated by acute kidney injury due to hypotension-induced acute tubular necrosis, for which he received hemodialysis for 2 weeks. Despite initial renal recovery, the patient's course was complicated again by acute kidney injury due to acute interstitial nephritis in the setting of vancomycin, requiring dialysis for 5 more days along with high-dose systemic steroids. Kidney function recovered, and the patient was discharged to a rehabilitation facility before returning home. Within 1 week of the patient returning home, rapidly expanding, painful plaques of retiform purpura of the bilateral proximal thighs developed. Cutaneous punch biopsy confirmed the diagnosis of calciphylaxis.**

# Epidemiology, Risk Factors, Presentation, and Pathophysiology

**.Calciphylaxis, also referred to as calcific uremic arteriolopathy, is a rare life-threatening vasculopathy that results from the deposition of calcium in the arteriolar microvasculature of the deep dermis and subcutaneous adipose tissue.**

**.Painful evolving lesions of livedo reticularis, livedo racemosa, and retiform purpura signify progressive cutaneous necrosis.**

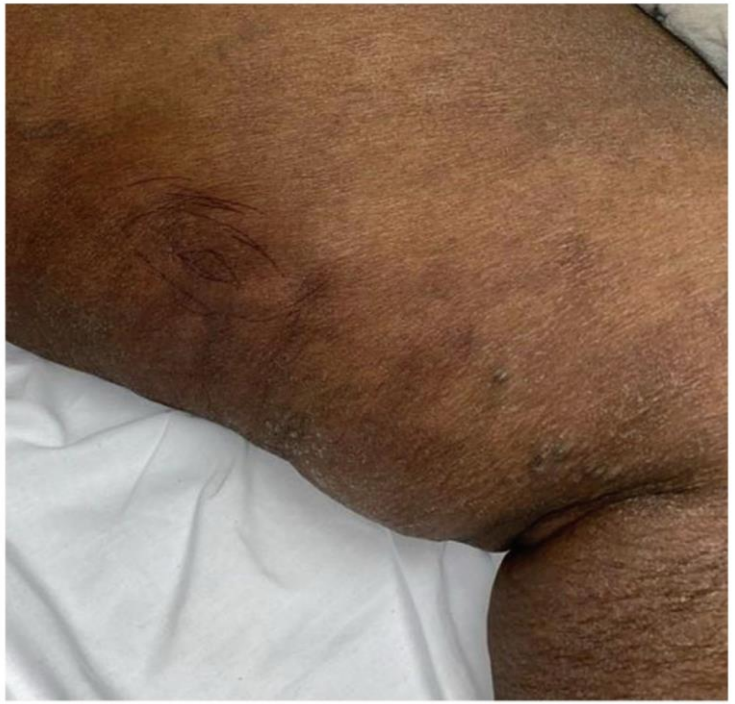

**Figure 1.** Exquisitely tender violaceous to hyperpigmented plaques and nodules of the posterolateral thigh; wedge excision demonstrated findings consistent with calciphylaxis.

# Epidemiology, Risk Factors, Presentation, and Pathophysiology

**. Sepsis from infection of cutaneous wounds is the leading cause of death in patients with calciphylaxi.**

**.Calciphylaxis is classically associated with chronic kidney disease (CKD).**

**Epidemiology :**

**.The largest nationwide study to date estimates an incidence rate of 3.49 per 1,000 patientyears among patients receiving maintenance hemodialysis.**

**.The incidence of calciphylaxis in this population has increased in the past decade.**

# Pathophysiology

**.In the setting of impaired kidney function, decreased synthesis of vitamin D along with compromised calcium reabsorption and phosphate excretion results in secondary hyperparathyroidism, which promotes bone remodeling, thereby increasing serum calcium levels and facilitating arteriolar microcalcification.**

**.Calciphylaxis may develop in patients with CKD despite normal serum calcium and phosphate parameters. Interestingly, polymorphism in vitamin D receptors has also been implicated in this syndrome.**

**.Calciphylaxis with concurrent nephrogenic fibrosing dermopathy has been reported in a patient receiving maintenance dialysis..**

# Risk Factors

**.In addition to ESKD, other notable risk factors for calciphylaxis include :**
**.Obesity**
**.diabetes mellitus**
**.female sex**
**.hyperparathyroidism**
**.warfarin**
**.corticosteroids**
**.vitamin K deficiency**
**.vitamin D deficiency**
**.hypoalbuminemia**
**.protein C and S deficiencies**
**.Crohn disease**
**.autoimmune disorders**
**.substantial weight loss**
**.recurrent hypotension**
**.malignant neoplasms (cholangiocarcinoma, hematologic malignancies, and melanoma)**

# Pathophysiology

**Recent case reports suggest that this rare depositional vasculopathy may appear in the context of early kidney injury, including acute kidney injury.**

# Pathophysiology

**.A case report described the bilateral appearance of calciphylaxis in the thighs of a woman 3 months after she experienced painless hematuria and nephrotic-range proteinuria in the setting of anti–glomerular basement membrane antibody disease.**

**.The specific pathogenesis of calciphylaxis remains to be fully elucidated.**

**.vascular wall depositions in calciphylaxis are exclusively composed of calcium apatite and organized circumferentially in small and medium-sized arteries, suggesting a pathophysiology distinct from that of atherosclerosis.**

# Pathophysiology

**.Although microvascular calcification is regarded as the main driver of pathogenesis, aberrant adipocyte proinflammatory cytokine signaling and recurrent vascular endothelial injury may also play roles.**

**.The notion that hypercoagulable states are important in the pathogenesis of calciphylaxis has been well described.**

**.A matched case-control study of 152 individuals with CKD identified that the presence of lupus anticoagulant, protein C deficiency, and combined thrombophilias were significantly associated with calciphylaxis. Furthermore, subsequent microvascular thrombosis may explain the characteristic exquisitely tender nature of calciphylaxis, as the presence of fibrin thrombi in skin biopsies has been associated with clinical pain severity.**

# Pathophysiology

**.Aberrations in molecular mediators that normally inhibit microvascular calcification have been implicated in the pathogenesis of calciphylaxis. For example, carboxylated matrix G1a protein (MGP) is an extracellular matrix peptide produced by vascular and endothelial cells that directly inhibits calcification.Fetuin A and pyrophosphate are additional inhibitors of calcification whose expression is decreased in CKD and calciphylaxis.Ultimately, low levels of MGP, fetuin A, and pyrophosphate result in a favorable environment for calcification to occur.**

# Presentation

**.Cutaneous examination of patients with calciphylaxis typically reveals exquisitely painful retiform purpura or tender nodules. Tender induration, hyperpigmented plaques, and hemorrhagic bullae are also reported.**

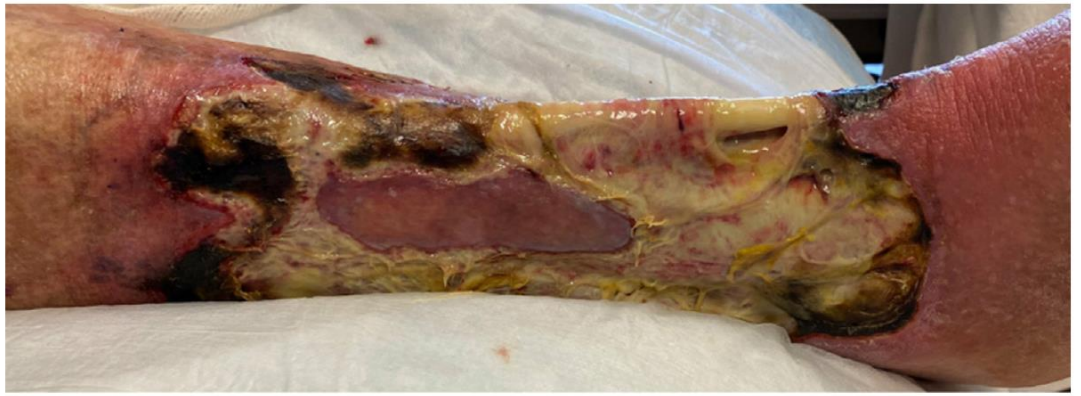

**Figure 2.** Distal lower-extremity retiform purpura with near-circumferential ulceration; punch biopsy revealed findings consistent with calciphylaxis.

# Presentation

**.most commonly seen on the abdomen and proximal lower extremities, calciphylaxis has been reported in relatively uncommon sites, including the penis, breasts, and digits. The presence of ulceration is associated with an increased mortality rate (Fig 3)**

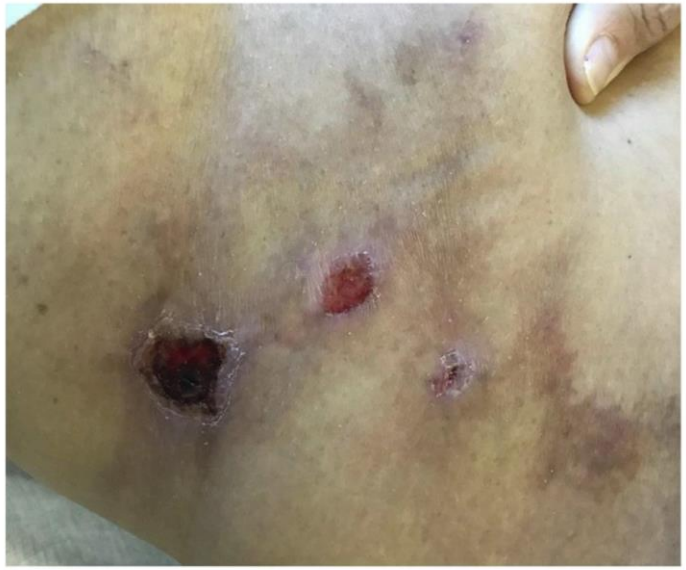

**Figure 3.** Hyperpigmented retiform patches and erosions in a patient with punch biopsy–proven calciphylaxis after 4 weeks of intravenous sodium thiosulfate; the patient had hepatorenal syndrome and had initially presented with painful ulcerating nodules.

# Presentation

**.Visceral calciphylaxis without primary cutaneous manifestations has also been reported, such as in mesenteric and colonic arteries.**

**.A recent retrospective chart review of 145 patients identified that, in 22 patients, the first calciphylaxis lesions appeared in areas of previous trauma, including direct injury from hitting an object (n = 4), abrasions (n = 3), insulin injections (n = 3), mechanical falls (n = 3), toe clipping or stubbed toe (n = 2), catheter placement (n = 1), and peritoneal dialysis catheter removal (n = 1)**

# Presentation

**.These findings support the hypothesis that calciphylaxis may be associated with the Koebner phenomenon (“Koebnerization”), a phenomenon in which dermatologic lesions emerge in areas of cutaneous trauma in otherwise intact skin.**

**At least one case report has described calciphylaxis in a recent surgical site, consistent with the hypothesis that Koebnerization may be an important risk factor.**

# Diagnosis of Calciphylaxis

**.diagnosis of calciphylaxis may be challenging.**

**.In patients with kidney disease, there should be high clinical suspicion of calciphylaxis after the appearance of painful nodules, indurated plaques, dusky livedoid plaques, and/or nonblanching retiform purpura.**

**.Calciphylaxis should still be suspected even if such lesions appear in sites other than the abdomen and lower extremities.**

**.retiform purpura is a cutaneous morphology that commands a broad differential; clinicopathologic correlation and judicious workup is necessary to rule out clinical mimickers.**

# Diagnosis of Calciphylaxis

**DDX :**

**.The most frequent initial diagnoses were cellulitis (31.0%), unspecified skin infection (8.0%), and peripheral vascular disease (6.9%)**

**.Other mimickers of calciphylaxis exist, including diffuse dermal angiomatosis, which may manifest as pink or hyperpigmented patches, retiform purpura, or ulceration in patients with ESKD.**

**.Skin biopsy may be useful in the diagnosis of calciphylaxis.**

# Diagnosis of Calciphylaxis

**Pathology :**

**.Punch biopsy rather than excisional biopsy is recommended to avoid nonhealing wounds even though it may not yield adequate tissue depth (Fig 4)**

**.Even if a negative punch biopsy result is obtained, empirical treatment with sodium thiosulfate is still recommended if clinical suspicion is high in view of the mortality associated with this condition.**

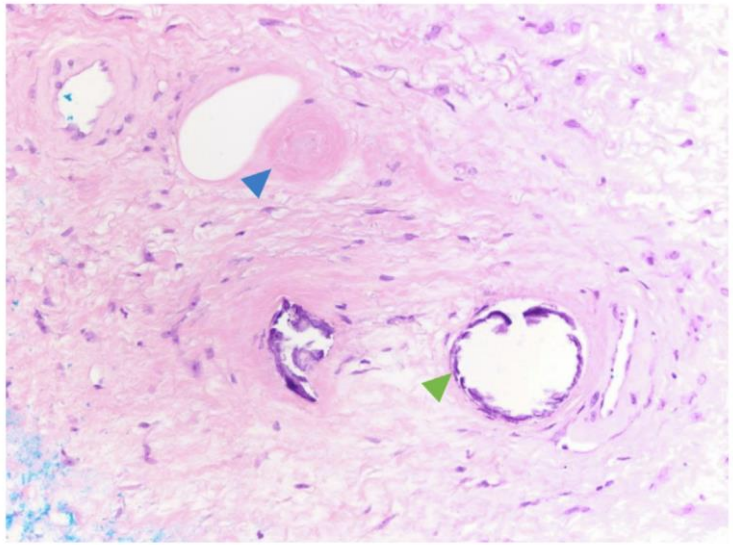

**Figure 4.** Biopsy-proven calciphylaxis. Circumferential, stippled basophilic deposits of calcium (green arrowhead) within dermal vessel wall with adjacent fibrin thrombus (blue arrowhead; hematoxylin and eosin stain; original magnification, ×200).

# Diagnosis of Calciphylaxis

**Pathology :**

**.Histopathologic findings may be subtle, and special staining (von Kossa) may aid in identifying stippled calcifications of small subcuticular vessels.**

**.calciphylaxis is characterized by calcification of deep dermis and subcutaneous tissue, along with fibrin thrombin and, occasionally, evidence of ischemic epidermal and dermal necrosis.**

.

# Diagnosis of Calciphylaxis

**.these findings are distinct from other forms of vessel calcification.**

**.For example, Monckeberg's sclerosis presents with medial calcification of small and medium-sized vessels that reduce vessel caliber, but there is no overlying epidermal or dermal necrosis.**

**.In classical atherosclerosis, intimal and subintimal lipid deposits and calcifications without skin necrosis are the dominant hallmarks.**

# Diagnosis of Calciphylaxis

**IMAGING :**

**.The role of imaging in the diagnosis of calciphylaxis has garnered attention, particularly when biopsy studies are inconclusive or invasive procedures are not possible.**

**.Plain radiographic findings that have been associated with calciphylaxis include the presence of small-vessel calcification and a netlike pattern of calcification.**

# Diagnosis of Calciphylaxis

**.Sonographic characteristics that have been associated with calciphylaxis include the presence of thin hyperechoic bands parallel to the epidermal surface, leading to a strong posterior acoustic shadow; hyperechoic spots with a narrow acoustic window; and linear hyperechoic bands parallel to the walls of a blood vessel with a narrow acoustic shadow.**

**.Plain radiographs and point-of-care ultrasound have been used to diagnose calciphylaxis in various settings, including emergency departments. Imaging may be especially important to make this diagnosis in anatomical sites that are challenging in which to perform a biopsy, such as the breasts .**

# Diagnosis of Calciphylaxis

**Serum markers :**

**.The predictive value of serum markers such as serum calcium, phosphate, parathyroid hormone, and albumin levels in the development of calciphylaxis remains an important question.**

**.Theoretically, these parameters could be useful in modifying hemodialysis strategies for patients who may be at a higher risk for the development of calciphylaxis. However, many patients with calciphylaxis may have an unremarkable calcium-phosphorus product. Further studies are needed to clarify if laboratory markers may be of diagnostic or risk-stratification utility.**

# Management of Calciphylaxis

**.There are no US Food and Drug Administration–approved treatments or uniform guidelines for the management of calciphylaxis.**

**.Management is a multipronged approach to:**

1. **mitigate risk factors**
2. **provide excellent wound care**
3. **optimize dialysis clearance**
4. **administer systemic medical therapies and analgesia.**

# Wound Care and Symptomatic Management

**.the current management of calciphylaxis relies on an interdisciplinary approach of experienced providers, including nephrology, dermatology, pain and palliative medicine, wound care, surgery, and nutrition.**

**.Vigilant wound care is paramount, with the main objectives of limiting necrotic tissue and preventing infection.**

**.Reported wound care modalities include enzymatic debridement, atraumatic debridement with sterile maggots, and judicious surgical debridement.**

# Wound Care and Symptomatic Management

**.Wound care may also optimize variables implicated in impaired wound healing, such as the reduced transcutaneous oxygen tension identified in lesions of Calciphylaxis.**

**In a retrospective study of 34 patients with calciphylaxis, half of the patients who underwent hyperbaric oxygen therapy had complete healing after 44 sessions of therapy over 2 months. These results provide evidence toward the potential use of hyperbaric oxygen in these patients.**

**.Nutritional support is also important in these patients to prevent protein loss associated with acute and chronic kidney disease.**

# Wound Care and Symptomatic Management

**.the severe pain associated with calciphylaxis often requires multimodal analgesia. Given that pain may be unresponsive to high-dose opioids, a pain-management consult may be beneficial to guide the administration of additional agents such as ketamine, benzodiazepines, or spinal anesthetic.**

**.Furthermore, a recent case report presented the effective use of cryoneurolysis of sciatic and pudendal nerves to manage intractable pain from calciphylaxis.**

# Pharmacotherapeutic Agents

**1.sodium thiosulfate**
**2. SNF472**
**3. Bisphosphonates**
**4. vitamin K**

# Pharmacotherapeutic Agents

**sodium thiosulfate:**

**.Intravenous sodium thiosulfate was first reported as a systemic treatment option for calciphylaxis in 2004.**

**Sodium thiosulfate reduces intravascular and extravascular calcifications by chelating calcium salts and forming a more soluble product, calcium thiosulfate.**

**.Intravenous sodium thiosulfate is also reported to reduce reactive oxygen species.**

**.Dosing of intravenous sodium thiosulfate is variable; a test dose of 12.5 g may be administered, followed by 25 g thrice weekly, but other dosing schedules have been reported.**

# Pharmacotherapeutic Agents

**.A study of 27 maintenance dialysis recipients treated with intravenous sodium thiosulfate showed complete remission in 52% of patients and partial remission in 19%.**

**.Another study of 53 patients receiving maintenance hemodialysis who were treated with intravenous sodium thiosulfate showed that 26% of patients had complete resolution and 19% had marked improvement in their skin lesions.**

**.a recent case report presented management of cutaneous calciphylaxis with small-dose fractionated sodium thiosulfate in a patient undergoing peritoneal dialysis.**

# Pharmacotherapeutic Agents

**.There remains a need for controlled study of the efficacy of sodium thiosulfate.**

**.Adverse effects include hypotension, metabolic acidosis, volume overload, hypocalcemia, and QT-interval prolongation.**

**.the adverse effects may be avoided if sodium thiosulfate is administered intralesionally as an alternative strategy for patients with early and limited disease or contraindications to intravenous therapy.**

# Pharmacotherapeutic Agents

**.A retrospective review comparing cumulative risk outcomes for patients with calciphylaxis receiving intralesional sodium thiosulfate revealed no difference in survival compared with dual therapy with intralesional and intravenous sodium thiosulfate.**

**.Intralesional injection frequency was variable, ranging from a single injection to an injection every few days; the median quantity of intralesional sodium thiosulfate per injection session was 3.0 mL.**

# Pharmacotherapeutic Agents

**SNF472:**

**.Another agent undergoing clinical trials for treatment of calciphylaxis is SNF472, which is a hexasodium salt of myo-inositol hexaphosphate.**

**.SNF472 is an inhibitor of vascular calcification, and it is currently in phase 3 clinical trials**

# Pharmacotherapeutic Agents

**Bisphosphonates:**

**. Bisphosphonates, which are pyrophosphate analogues, may offer therapeutic benefit for patients with calciphylaxis in the setting of ESKD.**

**. A prospective series of 11 such patients found that the addition of bisphosphonates slowed calciphylaxis progression in all patients 2-4 weeks after starting treatment and significantly improved outcomes compared with patients managed with supportive therapies only (debridement, low-calcium dialysate).**

# Pharmacotherapeutic Agents

**.Further investigations are indicated to understand the molecular pathways of the bone-vascular relationship and the efficacy of other bone-remodeling agents as potential treatments for calciphylaxis.**

**.Studies suggest that vitamin K may also play a role in the treatment of calciphylaxis.**

**.A retrospective cohort in France presented the use of vitamin K antagonists as one of the risk factors for the development of calciphylaxis in dialysis recipients.**

**.Vitamin K1 supplementation has also been shown to slow progression of preexisting coronary artery calcification.**

# Pharmacotherapeutic Agents

**.In patients with mild to moderate aortic valve stenosis, vitamin K1 supplements have also been associated with slowing progression of aortic valve calcification.**

**.a study of postmenopausal women found that vitamin K2 supplementation was associated with decreased aortic and common carotid stiffness.**

**.Given the evidence for the positive role of vitamin K in inhibiting vascular calcification, its current efficacy in calciphylaxis has recently undergone clinical trials. (table1)**

# Pharmacotherapeutic Agents



**Table 1.** Current and Recent Randomized Controlled Trials for Treatment of Calciphylaxis Indexed at ClinicalTrials.gov

| Trial | Interventions | Status |
|---|---|---|
| Better Evidence and Translation for Calciphylaxis (BEAT-Calci; NCT05018221) | Vitamin $K_1$, magnesium citrate, sodium thiosulfate, high-flux dialyzer, medium-cutoff dialyzer | Phase 3, recruiting |
| Efficacy of Lanthanum Carbonate in Calciphylaxis (NCT01289626) | Lanthanum carbonate | Phase 1, completed |
| Phase 3 Study of SNF472 for Calciphylaxis (Calciphyx; NCT04195906) | SNF472 | Phase 3, recruiting |
| Evaluation of Vitamin K Supplementation for Calcific Uremic Arteriolopathy (VitK-CUA; NCT02278692) | Vitamin K | Completed |
| Rheopheresis as Adjuvant Treatment of Calciphylaxis (RHEO-CAL; NCT04654000) | Rheopheresis | Not yet recruiting |

Information based on a search conducted May 19, 2022.

# Pharmacotherapeutic Agents

**. elimination of risk factors for calciphylaxis:**

**1.withdrawal of warfarin (vitamin K antagonist), vitamin D, and calcium-based phosphate binders.**

**2. Optimizing mineral bone disease (maintaining target ranges of calcium, phosphorus, and parathyroid hormone)**

**3. replacing activated vitamin D with cinacalcet to target the goal parathyroid hormone level, and parathyroidectomy for severe refractory hyperparathyroidism are reasonable approaches, as outlined by the KDIGO guideline.**

# Kidney Replacement Modality

**.Theoretically, increased clearance may improve calciphylaxis, given the usual resolution of mineral bone disease derangements (ie, hyperphosphatemia, hyperparathyroidism) after restoration of kidney function.**

**.For this reason, a multipronged treatment regimen has been advocated that includes increased dialysis dose, as reported in a home hemodialysis recipient who experienced complete healing of a large ulcer with dialysis 6 times per week.**

# Kidney Replacement Modality

**.Kidney transplant, the ideal kidney replacement therapy, resulted in full resolution of these calcific skin lesions in case series and in isolated case reports.**

# Palliative Care

**.Calciphylaxis is a debilitating condition associated with high morbidity and mortality rates.**

**.The use of palliative care provides a multidisciplinary strategy to address symptoms and goals of care for patients.**

# Conclusion

**.The consequences of unrecognized calciphylaxis can be devastating.**

**.it is imperative that calciphylaxis is always kept in a clinician's differential when managing patients with kidney disease who present with new painful skin lesions, even in the setting of acute kidney injury.**

**.A dermatologic evaluation, including a histopathological analysis, as well the use of radiographic tools, may be necessary to readily diagnose calciphylaxis.**

**.Ultimately, management of calciphylaxis requires a multimodal and interdisciplinary approach.**

# Conclusion

**.we would favor prioritizing pharmacotherapy with sodium thiosulfate, withdrawal of risk-inducing medications (warfarin, vitamin D, and calcium-based binders), cautious surgical debridement, cinacalcet or parathyroidectomy for those with poorly controlled hyperparathyroidism, and pain control.**

**.Increasing dialysis dose or performing transplant may be considered but may not be practical.**

**.Thoughtful experimental studies and controlled clinical trials are necessary for clarification of current unproven therapies so we can establish best practices for the treatment of calciphylaxis.**