

# **Calciophylaxis: controversies in pathogenesis, diagnosis and treatment**

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August 20, 2015**

***Disclosures / Financial Interests:*** This paper was conducted without funding or support by any outside entity. Furthermore, both authors affirm that there are no financial interests or other relationships with any commercial entities to disclose.

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**Purpose & Overview**

Calcific uremic arteriolopathy, otherwise known as calciphylaxis, is a rare disease characterized by skin ulceration and tissue necrosis, likely the result of vascular calcification with accompanying intimal hypertrophy and small vessel thrombosis. Although most often associated with end stage renal disease, it has also been seen in a number of other disorders (collectively referred to as non-uremic calciphylaxis). The purpose of this review is to summarize and analyze the currently available literature regarding the pathophysiology, risk factors, clinical presentation, diagnostic features, and treatment modalities for this exceptionally uncommon illness. A series of recommended treatments is proposed for optimal treatment of calciphylaxis lesions.

**Educational Objectives**

1. Know risk factors associated with calciphylaxis
2. Recognize the cutaneous features of calciphylaxis at each of its stages
3. Understand the variability of the histopathology of calciphylaxis and its limits in diagnosis
4. Understand the role of hypercoagulability in calciphylaxis and its effect on workup and treatment
5. Recognize the need for multi-specialty care in patients with calciphylaxis

## Introduction

Calcific uremic arteriopathy, also known as necrotizing livedo reticularis, but perhaps better known under the general term calciphylaxis, is a rare, oftentimes fatal complication usually associated with end stage renal disease (ESRD)<sup>i</sup>. It is characterized by skin ulceration and necrosis, primarily in the lower extremities leading to significant pain for afflicted patients. Histopathologic exam in these patients is often significant for medial calcification and intimal proliferation of small and medium-sized arteries leading to ischemic necrosis and secondary gangrene, although recent work has suggested far greater variability in histopathologic presentation<sup>ii iii</sup>, calling into doubt the utility of routine biopsies. Wounds are easily infected due to the loss of protective layers in the skin, leading to sepsis and death in up to 60% of patients within one year<sup>iv</sup>.

The typical cutaneous findings in calciphylaxis include tender, serpiginous, indurated plaques with overlying livedo racemosa as well as palpable subcutaneous masses, lesions that progress to non-healing ulcers covered by black eschar<sup>v</sup>. Primary areas of involvement include adipose-rich areas on the trunk and extremities, particularly the lower extremities; however, acral involvement, including penile<sup>vi vii</sup> and digital<sup>viii</sup> ischemia and necrosis has been well described. Rarer complications include cardiac<sup>ix</sup>, pulmonary<sup>x</sup>, and ocular<sup>xi</sup> involvement.

The incidence of calcific uremic arteriopathy has risen in the last decade, with some recent estimates as high as 5% of dialysis-dependent patients<sup>xii</sup>, but the true prevalence is likely unknown<sup>xiii xiv</sup>. Although primarily associated with chronic kidney disease, secondary hyperparathyroidism, and derangements in calcium and phosphate metabolism, calciphylaxis has also been diagnosed in patients with normal renal function, calcium, and phosphate pathways<sup>xv xvi</sup>. Other identified risk factors include female gender<sup>xvii</sup>, diabetes mellitus<sup>14</sup>, obesity<sup>xviii</sup>, and elevated calcium-phosphate product<sup>xix</sup>, among others<sup>xx xxi</sup>. Although highly correlated with end stage kidney failure, calciphylaxis is not thought to be an inevitable sequela of renal disease; as such, it is considered separate from renal anemia, hypertension, hyperparathyroidism, and osteodystrophy<sup>xxii</sup>.

The purpose of this review is to analyze the currently available literature regarding the pathophysiology, risk factors, clinical presentation, diagnostic features, and treatment modalities for this exceptionally uncommon illness. A series of recommended treatments is subsequently proposed for optimal treatment of calciphylaxis lesions.

## Pathophysiology

The term 'calciphylaxis' was first described by Selye et al, who applied it to a phenomenon observed initially in rodents, and described it as a hypersensitivity-like condition, wherein after a period of sensitization by a calcifying factor, second exposure resulted in local calcification with accompanying inflammation and sclerosis<sup>xxiii</sup>. Subsequently, similar lesions were reported in uremic human patients; these ischemic, ulcerated wounds were deemed sufficiently similar in morphology and other characteristics to the rats first described by Selye, and thus were termed lesions of calciphylaxis.

The process of vascular calcification is a closely regulated mechanism that depends on the active physiological management of calcium, phosphate, and PTH levels. It is the de-regulation of these processes that results in abnormal calcium deposition. Dystrophic vascular calcification is divided into two main categories, according to the location of the lesion and its association with atherosclerotic plaque formation<sup>xxiv</sup>. The more common version is calcification of the vascular intima, in conjunction with or secondary to the formation of atherosclerotic plaques. Conversely, the lesions of calciphylaxis are characterized by calcium deposition in the arterial media. However, both forms demonstrate calcium deposition in the form of calcium hydroxyapatite and the presence of matrix vesicles within the calcified vessel walls<sup>xxv</sup>.

Due to the association between calcium and phosphate regulation and the formation of calciphylaxis lesions, it is unsurprising that the majority of cases of calciphylaxis occur in those patients suffering from kidney disease, with prevalence rates of up to 5% reported in patients on long term dialysis<sup>12</sup>. Phosphorus, while an important component of cellular homeostasis, can rise to pathologic levels in impaired renal function due to impaired excretion, and has historically been noted to cause the expression of pro-calcific genes, with subsequent formation of a calcification prone matrix<sup>xxvi</sup>. Recent research has elaborated the process by which calcium is deposited in vessel walls further, while identifying more of the individual constituents involved. Under the currently accepted model for vascular calcification, lesion pathogenesis begins with the transformation of smooth muscle cells within the vessel wall into osteoblast-like phenotypes<sup>xxvii</sup>. This occurs through the interaction of some of the constituents of uremia – hyperphosphatemia, uremic toxins, and reactive oxygen species, and the decrease of Matrix Gla protein, a potent vascular calcification inhibitor; thus, to some extent, the progression of calciphylaxis is still heavily influenced by the functional state of the renal system. Prior research has posited that hyperphosphatemia serves as the trigger by which vascular smooth muscle cells ultimately begin transitioning to an osteoblastic cell type<sup>xxviii</sup>.

Additionally, bone morphogenetic protein-4, which is normally involved in bone repair and development, has been isolated in calciphylaxis lesions and is thought to promote calcification<sup>xxix</sup>. The activity of bone morphogenetic protein in catalyzing the formation of extra-skeletal calcification is dependent on the production of reactive oxygen species, which act through nuclear factor kappa B as an intermediary to spur the calcification process<sup>xxx</sup>.

At the same time, the role of hypercoagulability as a contributing factor in the development of calciphylaxis is gaining greater attention in the literature. Prior reports have demonstrated the formation of lesions in the setting of protein C and S deficiencies<sup>xxxi</sup>. Skin lesions in these cases were identical to calcific uremic arteriolopathy, but on laboratory analysis, up to 38% and 43% of reported cases had decreased levels of proteins C and S, respectively. The same study has reported cases of calciphylaxis in patients with antiphospholipid antibody syndrome, cryofibrinogenemia, and other hypercoagulable states. Evidence for the role of hypercoagulability in calciphylaxis is further supported by

histopathologic findings demonstrating thrombosis in 38 of 44 patients (86%) in one cohort, with no inflammatory infiltrates suggestive of a vasculitic process<sup>19</sup>.

Many studies argue that hypercoagulability in calciphylaxis may be a localized process mediated by cytokines including TNF- $\alpha$ , IL-1, IL-6. Together, these cytokines promote endothelial dysfunction and a procoagulant state through release of tissue factor, reduced endothelial cell protein C and protein S receptor expression and reduced production of natural vascular heparin-like molecules. The presence of a localized rather than systemic hypercoagulable state is also supported by the type and clinical distribution of lesions, which tend to be more acral in systemic hypercoagulable states.

## **Clinical Presentation**

### *History*

Patients presenting with calciphylaxis typically report significant pain and chronic, non-healing wounds as their primary complaints. The wounds themselves show signs of poor healing, including black eschar. Furthermore, the open, chronic wounds are often secondarily super-infected, leading to erythema, edema, purulent discharge, and other signs of a localized wound infection. Left untreated, these wounds can progress to systemic infections, with all of the associated complications and sequelae, including one-year mortality rates of up to 60%<sup>4</sup>. Although the cutaneous complications of calciphylaxis are often the patient's primary concern and thus tend to dominate the clinical presentation, vascular calcification has also been noted in skeletal muscle, brain, lungs, intestines, and other organ systems<sup>xxxii xxxiii</sup>, perhaps suggesting a systemic process rather than one exclusively limited to the skin.

There has been a significant effort toward understanding the clinical and patient characteristics that predispose patients to the development of calciphylaxis. Individual studies investigating these associations are often limited due to the sheer rarity of the disease, and thus prone to limitations in sample size, demographic heterogeneity, and selection bias. However, the summation of these works has revealed several recurring connections that strongly suggest that these factors contribute to the development of calciphylaxis.

The most commonly associated risk factors involve mineral components of the renal system, specifically phosphate, calcium, and the combined calcium-phosphorus product, as well as the factors that control serum levels of these minerals, namely parathyroid hormone and vitamin D. Initial investigation into calciphylaxis likely started with an analysis of factors that are common in patients with chronic kidney disease. It was a logical starting point, and initial investigations appear to support the hypothesis that these factors play a significant role in the development of calciphylaxis.<sup>xxxiv</sup> Although it is highly correlated with the presence of end stage kidney failure, calciphylaxis is not thought to be an inevitable sequela of renal disease; as such, it is considered separate from renal anemia, hypertension, hyperparathyroidism, and osteodystrophy.

In fact, a number of reports have described patients who developed calciphylaxis in the absence of mineral abnormalities, or even in the absence of renal failure. This phenomenon has been classified as non-uremic calciphylaxis. A systemic review of non-uremic calciphylaxis conducted by Nigwekar et al.<sup>31</sup> identified associations between calciphylaxis and the following medical diseases, chief among them primary hyperparathyroidism (27.8% of available cases), cholangiocarcinoma, CML, melanoma, and other malignancies (22.2%), alcoholic liver disease (16.7%), and connective tissue diseases (giant cell arteritis and rheumatoid arthritis – 11.1%).

There are a variety of medications associated with increased risk for developing calciphylaxis. Calcium supplements, calcium-based phosphate binders, and active Vitamin D inherently increase the available calcium for deposition, thus explaining their association<sup>17 19 xxxv</sup>. Other associated medications include corticosteroids, iron, teriperitide, and trauma related to subcutaneous insulin injections<sup>xxxvi</sup>.

Warfarin is one medication that has gained increasing awareness as a potential contributor to calciphylaxis, with multiple studies reporting this association<sup>xxxvii xxxviii</sup>. One case control study in Japanese ESRD patients found that warfarin therapy at the time of diagnosis was significantly associated with calciphylaxis (OR = 11.4, P = 0.0009). A similar study from a German registry note that approximately 50% of incident patients with calciphylaxis had been treated with Vitamin K antagonists<sup>22</sup>. These and other reports hypothesized that inhibition of vitamin K leads to under-carboxylation of Matrix Gla protein, a structure produced by vascular smooth muscle that serves as a potent inhibitor of vascular calcification in large arteries<sup>xxxix</sup>, although it may also contribute to thrombosis through inhibition of proteins C and S. Lack of Matrix Gla protein is thought to contribute significantly to medial calcification, and is thought to be one of the pathways by which warfarin promotes calciphylaxis. In animal models, deficiency or antagonism of Vitamin K2 (such as with Warfarin) in particular has been significantly associated with calcification of the arterial vasculature<sup>xl</sup>, presumably through lack of Matrix Gla.

In addition to these direct contributors to calciphylaxis, the disease has also been linked to a number of co-morbid conditions and demographic factors whose impact on the pathogenesis of arteriolar calcification is less well defined. Female gender, the co-presence of diabetes mellitus or obesity<sup>34</sup>, and a variety of autoimmune conditions such as lupus, antiphospholipid antibody syndrome, temporal arteritis, and rheumatoid arthritis have been linked to this disease<sup>xli</sup>, as well as end-stage liver disease and hypoalbuminemia. Although the mechanism behind the influence of these risk factors on the transformation of vascular smooth muscle into osteoblastic cell types involves a complex interplay of signaling molecules, one common end-point is thought to be upregulation of the NFKappaB pathway, which leads to increased expression of bone morphogenic protein 2<sup>12</sup>.

### *Physical Exam*

As noted above, the primary presentation of calciphylaxis is in the form of a symptomatic cutaneous lesion causing great pain and secondary infections. On physical exam, these lesions present as tender, serpiginous, indurated plaques with overlying livedo racemosa

as well as palpable subcutaneous masses, lesions that progress to non-healing, stellate-shaped ulcerations with black eschar over time. These wounds primarily involve the adipose-rich areas of the trunk, including the breasts, abdominal pannus, flanks, and lower back and buttocks, as well as the proximal lower extremities, in particular the medial and lateral aspects of the thighs and calves. However, multiple case reports have described an atypical presentation of calciphylaxis in the form of acral ischemia with both genital and digital involvement<sup>6-8</sup>.

## Differential Diagnosis

The differential diagnosis for calcific uremic arteriopathy encompasses diseases of both iatrogenic and organic etiology whose common presenting finding is the reticulated vascular prominence of vessels in the skin. The skin is nourished primarily by central arterioles that arise perpendicularly from vessels in the fascia, and each arteriole supports a 1- to 4-cm-diameter zone of the skin. Cyanosis resulting from the accumulation of deoxygenated blood at the junction between these vessels leads to the classic netlike pattern of lesions. There is a characteristic progression of lesions from the mottled, lace or net-like vascular pattern of livedo reticularis through the irregular, broken circles more reminiscent of forked lightning characteristic of livedo racemosa to finally, the branching purpuric lesions of retiform purpura, as determined by a combination of the severity of blood obstruction and the duration of blockage.

Warfarin-induced skin necrosis is difficult to differentiate clinically from calciphylaxis because the two diseases are indistinguishable. Very early findings may present a little differently, with petechiae, ecchymoses, and hemorrhagic bullae as opposed to the reticulated vascular pattern of calciphylaxis. However, the clinical presentation of both diseases converges upon the shared finding of painful full-thickness skin necrosis and the formation of stellate deep ulcers. Furthermore, like calciphylaxis, warfarin-induced skin necrosis tends to favor adipose-rich areas of the body, preventing clinicians from differentiating between the two diseases based on the distribution of lesions<sup>xlii</sup>. Histopathology is also largely non-diagnostic, because without the presence of calcium deposits in the subcutaneous tissue (discussed below), the typical findings of diffuse non-inflammatory dermal and subcutaneous microthrombi are components of both diseases.

In most cases, the only clinical point that allows differentiation between warfarin-induced skin necrosis and warfarin-induced calciphylaxis is the timing from medication administration to onset of the characteristic skin lesions. Skin necrosis from warfarin usually presents within the first ten days of drug administration, whereas calciphylaxis from warfarin tends to require a prolonged period of administration before lesion onset. However, clinicians should be counseled against using the timing of lesions as the definitive criteria for separating the two diseases, as there are multiple reports of late onset warfarin induced skin necrosis, typically due to inconsistent administration of the drug in non-compliant patients<sup>xliii</sup>. The etiology and unique distinguishing characteristics of other diseases with a similar clinical presentation to calciphylaxis are given in Table 1.

## Diagnostic Workup

The formal definitive diagnosis of calciphylaxis has traditionally necessitated a skin biopsy and can be considered when the clinical diagnosis is not clear. Biopsy can show medial calcification and intimal proliferation of small and medium-sized arteries leading to ischemic necrosis and secondary gangrene<sup>2</sup>. Other salient features include subcutaneous capillary calcification and thrombosis, extravascular soft tissue calcification, septal and lobular panniculitis, dermal-epidermal separation, and epidermal ulceration. Yield can often be increased through the use of special stains such as von Kossa or Alizarin red, which allow for better detection of microcalcification. In particular, perieccrine calcification on staining has been found to be highly specific for calciphylaxis<sup>2</sup>. Although calcification, when present, can aid greatly in solidifying the diagnosis of calciphylaxis, patients with all of the clinical characteristics of the disease can have biopsies that lack this feature on microscopic evaluation. One retrospective review of the histopathologic findings in 56 biopsies from confirmed calciphylaxis patients noted classic features of calcification in the internal elastic lamina of arteries in only 18% of samples, and even lower rates of calcification in the dermis, subcutaneous septae, and lobules (11%, 29%, and 16%, respectively)<sup>2</sup>.

The possible reasons behind this low sensitivity are multiple. First, the histopathology of early calciphylaxis may be as non-specific as demonstrating a thrombotic vasculopathy of the superficial dermal vessels, a finding that can be seen in many hypercoagulable conditions. Furthermore, the inherent limitations of biopsies, including limited depth of the specimen, sampling error in biopsy site, technical error during processing, and the clinical stage of the process at the sampled lesion itself contributes partly to this inability to make a firm diagnosis. Notably, the role of non-calcific processes in the development of calciphylaxis lesions may also play a key role in the lack of diagnostic findings in patients with all of the clinical exam findings of the disease. Specifically, the incompletely defined influence of hypercoagulability in the pathogenesis of calciphylaxis may help explain the variation in histopathologic findings. Further investigation into the histopathology of calciphylaxis is needed to better elucidate these associations.

Nevertheless, if a biopsy is pursued due to an unclear clinical diagnosis, the authors recommend an excisional biopsy at a site where the edge of the necrotic eschar, the livedoid area, and the indurated skin can all be simultaneously captured without compromising an excessive area of the skin. Alternatively, a 6 – 8 mm punch biopsy can also be considered, so long as an adequate sample of subcutaneous tissue can be obtained. If necessary, a telescoping 4 mm punch biopsy can be performed as a second stage procedure within the base of the large 6 – 8 mm punch biopsy location to obtain sufficient tissue for diagnosis. Due to the low yield of biopsy samples in calciphylaxis generally, and the extreme subtlety of early findings, it is important to have a pathologist or dermatopathologist with experience in diagnosing calciphylaxis review the sample.

The laboratory evaluation of a patient suspected of having calciphylaxis should consider two major goals: to assess for the presence of any potential risk factors and to rule out other vasculopathic or vasculitic disorders that may mimic the physical exam findings. These are presented in Table 2. The clinical utility of clinical imaging, chief among these

plain X-rays and three-phase nuclear bone scans, has been supported by some isolated studies<sup>xliv xlv</sup>. However, large-scale clinical trials for these diagnostic tools are currently lacking. Further evaluation of these tools in the diagnosis of calciphylaxis is likely necessary before they are recommended for inclusion in the routine workup of patients with suspected calciphylaxis.

## **Treatment of Calciphylaxis**

Calciphylaxis is, at its heart, a wide-reaching disease that involves the complex interaction of multiple organ systems. As such, the ideal treatment of this disease requires close and continuous collaboration amongst multiple specialties, among them dermatology, nephrology, wound care, nutrition, and pain management. The presence of additional comorbid conditions should lead providers to strongly consider close cooperation with cardiology, pulmonology, hematology, and other specialty physicians depending on the exact condition.

Many medical and procedural treatments have been proposed for the management of calciphylaxis. However, randomized, blinded studies have yet to be conducted on any of these treatment options, and the majority of reports currently supporting the use of these interventions come from retrospective case reports, case series, and cohort studies. Nevertheless, several of these treatment modalities appear to show great promise in the treatment of calciphylaxis based on preliminary studies, and are included here for consideration.

### *Sodium Thiosulfate*

Sodium thiosulfate has been shown to contribute significantly in treating both superficial and deep lesions associated with calciphylaxis, and as a result has become one of the primary treatment modalities for treatment of calciphylaxis lesions. Currently, the exact mechanism of action is unknown. Proposed hypotheses include vasodilatory and antioxidant properties, an increase in the solubility of calcium, or combination with calcium to form a dialyzable salt<sup>xlvi</sup>. Although intralesional (260 mg/mL) administration may be appropriate in isolated wounds, it is likely unfeasible in the presence of multiple lesions. Intravenous administration of sodium thiosulfate 25 grams three times weekly with dialysis sessions has also demonstrated good efficacy in the control and treatment of calciphylaxis<sup>xlvi</sup>, and may be a much more convenient delivery vehicle in the majority of afflicted individuals.

However, this treatment is not without its own pitfalls. The medication has been associated with some mild adverse effects, including nausea, vomiting, and headache, as well as severe metabolic acidosis<sup>xlvi xlix</sup>. However, the first three adverse effects often improve with subsequent infusions, and titrating the medication upwards from a low initial dose may be helpful in preventing these side effects. Although studies have not clearly demonstrated a statistically significant mortality benefit from this treatment, the largest case series demonstrated that 29 of 34 patients had improvement in lesions<sup>46</sup>. There are additional logistical concerns to take into account with this treatment as well. Due to the novelty of

sodium thiosulfate as a treatment modality for calciphylaxis, patients can experience great difficulty in obtaining this drug for outpatient treatment, as well as in locating a dialysis center comfortable with performing the infusions. Cost can be a barrier to successful treatment, as the monthly cost of IV sodium thiosulfate has been reported to approach \$10,000<sup>1</sup>.

### *Anticoagulation as a Standalone/Adjunct Treatment*

Theoretically, an argument can be made for the utility of anticoagulants as treatment modalities in the management of patients with calciphylaxis. As detailed above, there does seem to be interplay between calcific processes and hypercoagulability in the development of lesions in some patients, and others have developed lesions in the setting of a normal mineral bone disease axis. Furthermore, laboratory studies in certain patients have noted decreased levels of proteins C and S, or the presence of hypercoagulable states, and histopathology in these individuals reveals the presence of thrombosis without vasculitis.

Although patients with known hypercoagulable states and calciphylaxis may benefit from proper and adequate anticoagulation, full anticoagulation in all patients with calciphylaxis is not currently indicated due to the lack of efficacy, safety and non-warfarin options in patients with chronic kidney disease.

Nevertheless, Pentoxifylline, a methylated xanthine derivative with multiple immunomodulatory effects, can be considered an adjunctive agent due to its ability to reduce blood viscosity, decrease platelet aggregation, and thus mitigate thrombus formation<sup>li llii liii</sup>. Although its mechanism of action demonstrates some potential benefit, there are currently no validated studies outside of individual case reports documenting its efficacy. Further research is needed to elucidate the utility of anticoagulants as standalone or adjunct treatments in calciphylaxis patients without co-morbidities necessitating anticoagulation.

### *Anticoagulant Selection in Patients with Warfarin-Induced Calciphylaxis and Cardiac Co-morbidities*

Similarly, little information is available regarding anticoagulant selection in patients with co-morbidities necessitating chronic anticoagulation who subsequently develop calciphylaxis. Providing therapeutic anticoagulation in these patients is extremely difficult because the simultaneous presence of end stage renal disease, calciphylaxis, and cardiac co-morbidities necessitating chronic anticoagulation represents an intersection of medical diseases without clear treatment guidelines. Warfarin is often not tenable as a treatment modality due to its association with worsening calciphylaxis and alternative anticoagulants are largely prohibited due to declining renal function. In such cases, clinicians are often left balancing the morbidity inflicted by calciphylaxis against an elevated risk of fatal thrombosis should anticoagulation cease.

The American College of Chest Physicians (ACCP) publishes guidelines for anticoagulation in a variety of cardiac conditions. However, their recommendations are intended for

general anticoagulant coverage in patients with many different medical conditions. As a result, there are no specific protocols for this unique subset of patients with renal, cardiac, and dermatologic disease, and the broad rules proposed by the ACCP are largely inappropriate for these patients. For example, the ACCP often recommends warfarin as the anticoagulant of choice in many cardiac conditions requiring chronic anticoagulation. However, in patients with calcific uremic arteriolopathy, Warfarin should not be prescribed due to its link to the pathogenesis and acceleration of calciphylaxis lesions. In those for whom warfarin is contraindicated, the ACCP offers low molecular weight heparins as alternative anticoagulants. This is an untenable recommendation as low molecular weight heparins are largely contraindicated in renal failure due to increased bleeding risks.

In individuals with kidney disease, cardiac co-morbidities, and calciphylaxis who require long-term anticoagulation, there are two alternatives to warfarin: full-intensity subcutaneous unfractionated heparin (SQ UFH) and tinzaparin, a high molecular weight LMWH less dependent on renal clearance. Both are considered viable alternatives to warfarin for chronic anticoagulation<sup>liv lv</sup>. However, if unfractionated heparin is selected, providers should remain vigilant for signs of heparin-induced thrombocytopenia, a rare but present complication. Ultimately, hospitalization and a continuous UFH infusion may be the safest and most efficacious method of providing full anticoagulation while calciphylaxis lesions heal, but this must be weighed against the risk of nosocomial infection.

Finally, in all patients with calciphylaxis, a workup for the presence of an underlying hypercoagulable state should take place, as these diseases also place patients at greater risk for thrombotic events and possibly further progression of their calciphylaxis lesions. If an underlying condition such as antiphospholipid antibody syndrome is uncovered that mandates these patients begin chronic anticoagulation, we recommend full anticoagulation with a therapeutic agent other than warfarin (full intensity subcutaneous heparin, continuous heparin infusion, or tinzaparin, where available).

### *Correction of Underlying Calcium/Phosphorus Derangements*

Derangements of calcium and phosphorus regulation in renal failure, as measured by calcium, phosphorus, parathyroid hormone, and vitamin D levels, are seen as one of the primary associations predisposing patients to development of calciphylaxis. As a result, establishing adequate control over these abnormal processes through strict regulation of substrate levels can be an important adjunct treatment to minimizing the formation of lesions.

Sevelamer, a polyallylamine crosslinked to epichlorohydrin, is a phosphate-binding drug traditionally used to control phosphate levels in patients with chronic kidney disease<sup>lvi</sup>. Control of phosphate is critical given that high phosphate levels are currently hypothesized to be the metabolic trigger behind smooth muscle metaplasia into osteoblastic cell types. Also, because sevelamer helps reduce serum uric acid levels<sup>lvii</sup>, it may also play a role in reducing other mechanisms of lesion pathogenesis. An alternative method for maintaining tight control of serum levels of the substances mentioned above may be through intense hemodialysis in excess of those provided at typical dialysis sessions. Although the schedule

for intense hemodialysis can vary by center, increased length and/or frequency of dialysis could function to keep serum levels within a narrow therapeutic window, thereby reducing the incidence of calciphylaxis, limiting lesion progression, and promoting shorter healing times. Additionally, evidence suggests other benefits to intense hemodialysis, including better blood pressure control and improved quality of life<sup>lviii</sup>.

Vitamin K, as mentioned above, also plays a key role in the gamma-carboxylation of Matrix Gla protein, a major inhibitor of vascular calcification. This lack of active vitamin K-dependent matrix Gla has been documented in dialysis patients, and these individuals have been found to demonstrate increased levels of the inactive form of this protein<sup>lix</sup>. As a result, iatrogenic administration of vitamin K2 (menaquinone) may help improve the calcification inhibitory activity of this protein.

Bisphosphonates are a well-studied and frequently administered treatment for the mitigation of bone loss and prevention of hypercalcemia, especially in diseases where calcium levels are elevated through the action of parathyroid hormone on osteoblasts and the subsequent acceleration of bone resorption through the activation of osteoclasts. Parathyroid hormone has been identified as a significant risk factor for the development of calciphylaxis, as mentioned previously. In such cases, bisphosphonates may contribute to the maintenance of normal calcium levels by blunting the effects of parathyroid hormone. In fact, bisphosphonates have demonstrated an ability to facilitate healing of calciphylaxis lesions regardless of parathyroid hormone levels. Authors have proposed a number of hypotheses regarding the mechanism of action of these medications in promoting healing in calciphylaxis. These include modification of calcium hydroxyapatite formation, binding of bisphosphonates to vascular smooth muscle cells that mimic osteoclasts and osteoblasts in phenotype, and many others; however, the true mechanism is currently unknown<sup>5</sup>.

In patients with calciphylaxis where it appears vascular calcification is driven by parathyroid hormone, cinacalcet is the preferred treatment for secondary hyperparathyroidism. Parathyroidectomy should be reserved for patients with calciphylaxis that fail medical management of hyperparathyroidism. Reports of parathyroidectomy in calciphylaxis have had mixed outcomes<sup>lx</sup> due to the significant risks associated with surgery, especially in medically complicated patients such as those that traditionally suffer from calciphylaxis.

### *Kidney Transplantation*

The utility of kidney transplantation remains unclear in the treatment of calciphylaxis. Because uremic calciphylaxis develops largely from derangements of the mineral bone disease axis secondary to an improperly or non-functioning kidney, the correction of these imbalances through transplantation of a working donor kidney should theoretically restore mineral levels to their prior baselines and prevent the development or progression of calciphylaxis.

However, in practical application, this does not appear to be the case, as reports noting both the resolution of calciphylaxis and new onset of calciphylaxis after transplantation

exist<sup>lxi lxii</sup>. Whether this is due to irreversible changes in vascular smooth muscle metaplasia that are not undone through transplantation, or the influence of hypercoagulability or other pathologic processes is currently unclear, and more work is necessary to resolve these uncertainties.

### *Wound Care*

Because of the significant risk of infection in patients with calciphylaxis, meticulous wound care should represent a cornerstone of therapy in those with this disease. Goals of appropriate wound management should include: removal of necrotic tissue, aiding wound healing, and preventing infection. Gentle debridement of necrotic tissue is recommended to allow proper wound healing, but is best done when there are no longer signs of active calciphylaxis such as surrounding livedo<sup>34</sup>. Additionally, deep or wide surgical debridement and skin grafting is controversial but can be considered on a case-by-case basis due to risk of worsening as well as poor wound healing<sup>28</sup>. Ideally, dressings should provide a moist environment to promote healing and remove excess exudates. Simultaneously, a dressing that is easy to apply and remove has been found ideal to reduce the incidence of surrounding skin trauma<sup>28</sup>. The exact type of dressing best suited to any individual lesion should be left to the discretion of the provider<sup>lxiii</sup>, but the choice of dressing should reflect the priorities listed above. Additionally, a nutrition consult to address malnutrition should be obtained. If patients are not able to improve dietary intake, consideration should be given to nutrition by gastric tube and parenteral nutrition.

Other adjunct therapies thought to promote enhanced wound healing are hyperbaric oxygen and maggot debridement. A group of 46 individuals represents the largest cohort of patients with calciphylaxis treated with hyperbaric oxygen<sup>lxiv</sup>, and in that group, 58% of those who received a full course demonstrated improvement in wound scores, and half of those progressed to complete healing of wounds. Maggot therapy may be another adjunct treatment for providing gentle debridement of necrotic tissue, preventing systemic infection, and thereby promoting wound healing. To date, only isolated reports on the successful use of maggot debridement therapy in calciphylaxis exist<sup>lxv</sup>.

Similarly to skin grafting, only isolated reports of successful revascularization surgery in calciphylaxis exist in the literature<sup>lxvi lxvii</sup>. An evaluation for peripheral vascular disease in calciphylaxis patients, especially those presenting with acral necrosis, is warranted to assess whether revascularization might be indicated. However, insufficient evidence exists to make firm recommendations regarding the utility of revascularization in promoting wound healing in calciphylaxis. Notably, however, the very need for vascular procedures has been associated with poor survival in calciphylaxis patients<sup>lxviii</sup>; it is unclear what influence the procedure itself may have played in affecting these morbidity figures. This evaluation and any subsequent management should occur in collaboration with a vascular surgeon, or in the case of penile calciphylaxis, a urologist.

### *Pain Control*

Given the high levels of pain experienced by patients with calciphylaxis, appropriate pain control and other palliative measures are warranted as valuable components of therapeutic management. Although narcotic analgesia for pain control is recommended, morphine is thought to cause toxic accumulation of toxic by-products that further compromise tissue perfusion. Fentanyl patches may be preferred for baseline pain control as a result<sup>5</sup>, but this should be supplemented with additional hydromorphone for breakthrough pain or wound dressing changes.

### *End of Life Discussions*

The prognosis for patients with calciphylaxis is grim, with overall one-year survival rates failing to reach 50% (45.8%) in at least one major study, and two-year survival rates approaching 20%<sup>19</sup>. Patients already on dialysis at the time of diagnosis were noted to have reduced median survival (2.4 months) compared to non-dialysis patients with calciphylaxis (8.4 months). Although no significant difference in survival was noted based on lesion distribution (proximal vs. distal), those with both distal *and* proximal disease appear to suffer from higher mortality, most likely due to the increased burden of disease (44.7%, 32.2%, 12.5% 1-year survival rates, respectively), a finding that will require additional studies with larger cohorts to confirm. Most notably, compared to patients on dialysis without calciphylaxis, the Kaplan-Meier survival rates at 1, 2, and 5 years for those on dialysis with calciphylaxis are markedly reduced (29%, 14.5%, and 9.1% vs. 88.1%, 74.4%, and 46.9%).

Due to the intense pain and morbidity suffered by those with progressive and unresolving calciphylaxis lesions, as well as the marked decrease in survival as a result of the disease, an early discussion with patients and their families regarding their prognosis and approach to future therapy is warranted. Some patients may desire to stop hemodialysis and other adjunct therapies rather than deal with excruciating pain in the setting of an unfavorable prognosis. As a result, we recommend these discussions take place almost immediately after patients have had an opportunity to process the impact of their diagnosis and become ready to discuss their management going forward.

### *SNF and LTAC Issues*

The long-term management and care of many patients with calciphylaxis is likely to occur at skilled nursing facilities and other long term acute care centers specialized for this purpose. Although these locations are designed for patients with serious medical problems that require intense treatment for extended periods of time, they are likely not trained or equipped to deal with the unique intersection of diseases many calciphylaxis patients suffer from. Dedicated in-house wound care nurses are often not present, and contracted providers who perform this function often do not visit with the frequency necessary for the optimal treatment of calciphylaxis patients.

Finally, the physicians on staff at these locations, who become the primary providers for patients who enter long term acute care centers, may not be intimately familiar with the management of patients with calciphylaxis due to its sheer rarity. These physicians would

also become responsible for coordinating care between multiple specialty providers (dermatology, cardiology, nephrology, hematology, palliative care, pulmonology, hematology, and pharmacy, depending on the patient's unique circumstances). Transportation to and from physicians in each specialty who are comfortable dealing with organ-specific manifestations of calciphylaxis is daunting, and is often impossible if the clinic is outside the range of where a SNF/LTAC can transport the patient.

### *Recommendations*

Based on this review of the pathogenesis of calciphylaxis, the clinical history and physical exam findings of afflicted patients, and the currently available list of medications and other therapeutic modalities, the following steps are recommended for the management of patients with calciphylaxis.

First, treatment should begin based on clinical suspicion initially, and should continue if biopsy findings are inconclusive, as calcium deposition and thrombosis may not always be seen. Intravenous thiosulfate should be initiated immediately, preferably at a dosing regimen of 25 grams three times weekly with dialysis sessions, although other vehicles of administration (intralesional) might be considered under appropriate circumstances. Sodium thiosulfate has become a critical component in the effective management of calciphylaxis in recent years, so much so that clinicians should consider delaying patient discharge until appropriate outpatient sources can be procured to ensure continuous therapy.

Many of the adjunct therapies mentioned above, chief among them calcium-free phosphate binders, intensive hemodialysis or low calcium hemodialysis, meticulous wound care, and appropriate pain management should be simultaneously initiated in all patients. More specialized treatment modalities, including cinacalcet, bisphosphonates, hyperbaric oxygen, and parathyroidectomy should be tailored to individual patients on a case-by-case basis, and are discussed in further detail above. Surgical or maggot debridement of wounds should be considered when there are no signs of ongoing ischemia. As noted previously, there are no randomized, blinded studies for any of these treatment options. Often, disease can still be active and can continue to progress if a patient is discharged too quickly from the hospital. Ideally, a patient should not have signs of active ischemia (livedo, induration, and/or severe pain) when discharged.

At this time, there is insufficient evidence of successful treatment using anticoagulants in patients without indications for anticoagulation to justify their inclusion as adjunct or standalone treatments. As a result, in the general case we do not recommend the routine administration of anti-platelet agents or other medications designed to counteract the clotting or thrombotic cascade for the treatment of calciphylaxis. The one exception may be pentoxifylline, which may be considered an option due to its low side effect profile.

Regarding full anticoagulation in patients with renal failure, cardiac co-morbidities, and/or chronic venous thromboembolic disease necessitating long-term anticoagulation, and calciphylaxis precluding the use of warfarin, evaluation should begin with an assessment of

the patient's indication for warfarin to determine whether discontinuation is possible. In those patients where chronic anticoagulation is necessary, full-intensity SQ UFH or tinzaparin may function as viable alternatives. If providers are reluctant to prescribe SQ UFH, then hospitalization with continuous UFH infusion as an inpatient is another method to provide therapeutic anticoagulation while evaluating for wound stabilization and improvement. Low molecular weight heparins should, at best, serve only as treatments of last resort in close collaboration with multiple subspecialties and with strict aPTT/anti-Factor Xa monitoring<sup>lxix</sup>. Any patients in which warfarin must be continued as the anticoagulant of choice should be monitored closely for new lesions while continuing treatment with all of the other components of calciphylaxis treatment (sodium thiosulfate, sevelamer, etc.).

However, we do recommend a full laboratory examination for underlying causes of hypercoagulability such as antiphospholipid antibody syndrome, protein C and S deficiencies, and other diseases that markedly increase the risk for thrombosis. If such a condition is uncovered, then it may be appropriate to discuss the possibility of anticoagulation with pentoxifylline, full intensity subcutaneous heparin, tinzaparin, or other treatment modalities.

## **Conclusions**

Calciphylaxis is an ischemic small-vessel vasculopathy with a controversial, multi-factorial pathogenesis often seen in patients with ESRD on hemodialysis. Additional co-morbidities and the administration of certain medications, chief among them warfarin, can accelerate lesion formation and complicate attempts at treatment. This report reviews the pathogenesis, risk factors, clinical history, physical exam findings, diagnostic evaluation, and treatment of calciphylaxis as it is currently understood. In doing so, we hope to illustrate the far-reaching scope of the disease, the complex interaction that results in multiple organ systems, and the many dilemmas clinicians can face when managing this disease. Ultimately, successful treatment of calciphylaxis is a multi-disciplinary effort, and should involve close collaboration between dermatology, cardiology, nephrology, hematology, palliative care, pulmonology, hematology, pharmacy and the primary treatment team as necessary depending on the unique manifestations of disease in individual patients.

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## Tables

Table 1: Differential Diagnosis for Calcific Uremic Arteriolopathy (Calciophylaxis)									
Disease	Antiphospholipid Antibody Syndrome	Heparin Skin Necrosis / HIT	Purpura Fulminans (DIC) & TTP	Cold-Precipitating Proteins	Peripheral Artery Disease	Medium/Small Vessel Vasculitis	Stasis Ulcers	Traumatic Ulcer	Neuropathic Ulcer
	Skin involvement NOT part of diagnostic criteria	Begins < 2 weeks after Heparin initiation	Fulminant skin necrosis in setting of DIC	Type I Cryoglobulins and cryofibrinogens = acral / medial and lateral thigh involvement	Claudication, weak pulses, abnormal ABI	ANCA associated vasculitis (PAN, Levamisole, Autoimmune, Buerger's)	Located on medial malleolus	History of trauma	Punched-out
	Widespread Necrosis < 25 Cases	Lesions tend to occur at injection sites	Widespread: starts acral, progresses proximally	Labs: SPEP/UPEP = M-spike	Punched out, dry ulcers on extremities	+ P-ANCA, C-ANCA, MPO, PR3, other antibodies	Irregular, not stellate-shaped wounds	Irregular shape	Ulcers located on pressure points
<b>Key Points</b>	Catastrophic APLS = multi-system involvement	Platelet count fall > 50% (and high 4T score)	Microangiopathy and thrombocytopenia on laboratory evaluation	Pathology = thrombotic vasculopathy	Pathology: intimal fibrosis, medial calcification	Multi-system involvement	Wet wounds (fibrinous exudate)	No livedo	Surrounding callus
	+ Lupus Anticoagulant	+ Antibody against heparin-PF4 complex	TTP = normal coagulation values	PAS Stain = can show cuffing around small vessels		+ Cocaine ingestion (levamisole vasculitis)	Varicose veins, hemosiderin deposits		Neurologic exam abnormal
	+ Anti-cardiolipin Antibodies	+ Serotonin Release Assay	DIC = deranged coagulation values	Mixed cryoglobulins = leukocytoclastic vasculitis (palpable purpura)			No surrounding livedo		

**Table 2: Laboratory Evaluation of Patients with Calciphylaxis**

Labs to Evaluate for Risk Factors			Labs to Rule Out Other Diseases	
<i>Kidney Damage</i>	<i>Mineral Bone Disease Axis</i>	<i>Infectious Workup</i>	<i>Hypercoagulability</i>	<i>Other Processes</i>
Serum urea nitrogen	Calcium	Complete blood cell count	Protein C	ANCA's (IF and ELISA)
Creatinine	Phosphorus	CBC differential	Protein S	Antiphospholipid Antibodies
Estimated glomerular filtration rate	Alkaline phosphatase	Blood cultures	Antithrombin III	SPEP/UPEP
Urinalysis*	Parathyroid hormone	C-reactive protein	Antiphospholipid antibody	Cryoglobulins / Cryofibrinogens
Protein-creatinine ratio*	Vitamin D	Albumin	Prothrombin time	RF
24-hour urine collection*	Calcium-phosphorus product	Other inflammatory markers	International normalized ratio	Vascular Studies (ABI, Arterial Duplex, CTA with Run-off)**
			Partial thromboplastin time	Malignancy**

\* = additional parameters for non-dialysis patients

\*\* = evaluation should occur based on clinical suspicion and/or abnormalities in other markers indicative of these processes