Calciphylaxis: A systematic review of existing and emerging therapies

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Calciphylaxis, also known as calcific uremic arteriolopathy, is a cutaneous ischemic small vessel vasculopathy seen in 1 to 4% of patients with chronic kidney disease on hemodialysis. It is associated with extreme pain and a 60 to 80% mortality rate in the setting of few and frequently ineffective therapeutic options, although this may be changing based on reports of success with newer therapies. (J Am Acad Dermatol 2012;67:e253-60.)

INTRODUCTION

Calciphylaxis, also known as calcific uremic arteriolopathy, is a cutaneous ischemic small-vessel vasculopathy seen in 1% to 4% of patients with chronic kidney disease (CKD) on hemodialysis.[1-4] It is associated with extreme pain and a 60% to 80% mortality rate in the setting of few and frequently ineffective therapeutic options, although reports of successful treatment with newer therapies exist.[3,5,6]

Multiple reports have recently documented successful treatment of calciphylaxis with sodium thiosulfate, bisphosphonates, or cinacalcet. Herein we review these newer approaches along with other treatment modalities for calciphylaxis.

Abbreviations used:

CKD:	chronic kidney disease
FDA:	Food and Drug Administration
HBO:	hyperbaric oxygen
PTH:	parathyroid hormone
STS:	sodium thiosulfate

BACKGROUND

Calciphylaxis was first described in 1962 as multiple-organ calcification and necrosis in laboratory rats sensitized with "calcifiers," or by the induction of renal failure.[7,8]

Chiefly seen in patients with CKD, particularly those patients on hemodialysis,[4] calciphylaxis was previously described as a rare phenomenon. However, recent work suggests the incidence may have increased to 5% or more in dialysis-dependent patients.[9,10] Factors implicated in the development of calciphylaxis in this population include hypercalcemia, the use of calcium-containing phosphate binders, vitamin D therapy, hyperphosphatemia, elevated calcium-phosphate product, and secondary hyperparathyroidism.[10,11] Female gender, Caucasian race, obesity, diabetes mellitus, warfarin use, hypercoagulability, hypoalbuminemia, albumin infusion, and trauma also increase the risk for the development of calciphylaxis.[1,3,12,13]

Calciphylaxis has also been observed in nonuremic populations. Risk factors in the absence of CKD include primary hyperparathyroidism, alcoholic liver disease, malignancy, connective tissue disease, prior corticosteroid use, and protein C or S deficiencies.[14]

While the exact pathogenesis of calciphylaxis remains unclear, histopathological findings include small vessel endovascular fibrosis, fibrin thrombi, intimal proliferation, obliterative vasculopathy, tissue ischemia, calcification, panniculitis, and subcutaneous fat necrosis.[9,14,15]

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Prognosis is often poor, with proximal calciphylaxis affecting the abdomen, thighs, and buttocks, thereby resulting in a 63% mortality rate.[6,16] Distal calciphylaxis is associated with a lower mortality rate, reported as 23% in one study.[6]

The resultant painful ischemic ulcerations, as well as an estimated 60% to 80% mortality rate, underscore the need for effective therapeutic options for calciphylaxis.[3,5,6]

CAPSULE SUMMARY

- Calciphylaxis is known to have a high morbidity and mortality rate with few effective therapeutic options.
- This review outlines the current status of existing and newer therapies for calciphylaxis, including success rates, purported mechanisms of action, and potential adverse effects.
- A suggested treatment approach based on a systematic review of the latest literature is provided.

METHODS

PubMed electronic searches were performed by using combinations of the following terms: "calciphylaxis," "calcific uremic arteriolopathy," "hyperparathyroidism," "non-uremic," "treatment," "therapeutics," "sodium thiosulfate," "cinacalcet," "bisphosphonates," "hyperbaric oxygen," and "parathyroidectomy." We systematically reviewed the resulting works as well as relevant articles cited in their reference sections, considering only literature written in English.

PREVENTION

Given the high risk of recurrent infections and sepsis after the onset of calciphylaxis, prevention is preferable to treatment. In patients on hemodialysis, low-calcium dialysate may be helpful. This has been advocated for the treatment of calciphylaxis after onset, although the efficacy in the context of prevention remains unproven.[9,15,17] New, lower target values for serum phosphate (3.5-5.5 mg/dL), serum calcium (8.4-9.5 mg/dL), and parathyroid hormone (PTH, 150-300 pg/mL) recommended by the National Kidney Foundation may help prevent calciphylaxis in patients on hemodialysis.[2,18] In addition, a calcium-phosphate product less than 55 mg^2/dL^2 may also be protective.[2,19] Caution with vitamin D and calcium supplementation with close monitoring of calcium, phosphorus, and PTH homeostasis is recommended.[3,20,21] Because hypoalbuminemia is a risk factor for calciphylaxis, attention to nutritional status and the judicious provision of albumin infusions when necessary may also help, bearing in mind that albumin infusion itself has been implicated as a risk factor for calciphylaxis in some reports.[2,3,16,22] Other reports note that the antioxidant properties of serum albumin may mitigate systemic inflammation and ischemic damage in calciphylaxis.[3,23]

Clinicians may help patients intervene on modifiable risk factors such as diabetes mellitus and obesity with blood glucose control and weight loss, noting that rapid weight loss may induce calciphylaxis.[14,24] Patients with chronic renal insufficiency having disease-state risk factors (obesity, diabetes mellitus, primary or secondary hyperparathyroidism, alcoholic liver disease, malignancy, connective tissue disease, and protein C or S deficiencies) or with demographics identified as risk factors (female gender, Caucasian race) warrant both control of serum calcium and phosphorus and monitoring for signs and symptoms of calciphylaxis. At-risk patients should avoid cutaneous trauma (such as subcutaneous injections of insulin or heparin) at sites predisposed to developing calciphylaxis, including the buttocks, thighs, and abdomen.[20] Because of the ischemic mechanism involved, hypotension may exacerbate cutaneous hypoperfusion and predispose to calciphylaxis, mandating that clinicians assess for and treat hypotension in these patients.[1,20,25,26]

MEDICAL THERAPIES

Sodium thiosulfate

Originally used as an antidote in the treatment of cyanide toxicity and more recently to treat nephrogenic systemic fibrosis and recurrent calcium urolithiasis, as well as to prevent ototoxicity in carboplatin recipients, sodium thiosulfate (STS) has captured new interest in the treatment of calciphylaxis.[27-31] At least 21 patients in the published literature have responded to intravenous or intraperitoneal STS since the first report in 2004.[12,32-52] In addition, therapeutic success with STS was reported in as many as 30 calciphylaxis patients in 2009 alone at the 29th Annual Dialysis Conference.[32] Rapid relief of ischemic pain within days to weeks is frequently reported in patients receiving STS, with wound healing taking 8 weeks or longer.

While there is no standardized dose of STS for calciphylaxis, reported effective doses range from 5 to 25 g administered intravenously 3 times weekly, typically during or after hemodialysis in patients with CKD.[12,41,42,45] Hayden et al recommend 25 grams of STS IV during dialysis, with an initial test dose of 12.5 grams per 100 mL of normal saline infused over

1 hour.[12] The total duration of therapy varied per patient, but the authors recommended that STS administration continue for at least 2 months beyond complete healing of ulcerations.[12] At an estimated $50 per 25 grams of STS, the average cost of this regimen is approximately $600 monthly.[12] Neither Medicare nor Medicaid universally reimburse the cost of STS for calciphylaxis.[53,54]

While many reports note favorable outcomes with STS, the literature documents at least 3 patients treated with STS who ultimately died of sepsis.[21] Notably, all 3 patients were undergoing peritoneal dialysis.[21,55-57] While the majority of case reports documenting successful treatment using STS have involved patients on hemodialysis or continuous venovenous hemodialysis, at least one patient on peritoneal dialysis achieved a favorable outcome.[33] Furthermore, STS has also been used successfully in patients with non-uremic calciphylaxis.[45,58]

Sodium thiosulfate is thought to be effective in treating calciphylaxis by several mechanisms: antioxidation, vasodilation, and chelation. The compound acts as an antioxidant in several ways, including scavenging reactive oxygen species implicated in the pathogenesis of calciphylaxis and generating glutathione.[34,59] Sodium thiosulfate is also thought to recouple endothelial nitric oxide synthase, contribute to the reduction of oxidized hydrobiopterins, and generate hydrogen sulfide, each of which promotes local vasodilation.[21,34,59] The rapid pain relief often reported with STS may be attributable to vasodilation by these mechanisms at the peripheral neuronal endoneurium.[60] Chelation of intravascular and intraparenchymal calcium salts with STS yields calcium thiosulfate, which is significantly more soluble than other calcium salts.[21] This gradual dissolution of calcium salts, followed by removal via dialysis, is the purported mechanism by which STS eliminates calcium deposits over weeks to months.[33,60] Therapy with intravenous STS is associated with the risk of nausea, vomiting, headache, and rhinorrhea.[21] The most important potential adverse effect associated with STS is anion gap metabolic acidosis due to the resulting presence of thiosulfuric acid.[42] This gap acidosis may result in deleterious effects on protein and bone metabolism, the requirement of oral sodium bicarbonate to correct the acidosis (possibly presenting an unacceptable sodium load), or development of hypocalcemia, which may result in a prolonged QT interval.[42,61]

Despite marked favorable attention recently, no prospective, randomized controlled trials of STS in calciphylaxis have yet been completed. In addition, many reported cases involve the use of multiple therapies along with STS; in this context, it is difficult to attribute successful therapy to STS alone.

Bisphosphonates

Bisphosphonates are frequently used to treat osteoporosis, malignant hypercalcemia, Paget's disease of the bone, and bone metastasis.[21,62] Monney et al[63] first used intravenous pamidronate to successfully treat calciphylaxis, resulting in resolution of pain within 2 days and ulcer healing over 6 weeks.[64] Since then, 5 additional patients have responded to intravenous pamidronate, intravenous ibandronate, or oral etidronate.[65-69] Rapid, dramatic pain relief was achieved in 3 of these 6 patients over several days.[63,65,69] Complete ulcer healing took up to 6 months.[68,69]

Bisphosphonates are known to inhibit osteoclasts through several well-described mechanisms.[70] While resulting changes in calcium, phosphate, and bone metabolism may solubilize and mobilize intravascular calcium over time in calciphylaxis, they are unlikely to explain the rapid resolution of symptoms demonstrated in the aforementioned case reports.[15] Instead, the involvement of bisphosphonates in macrophage inhibition and suppression of inflammatory cytokine release may be responsible for the expedient pain relief noted above.[71,72]

Adverse reactions to bisphosphonates include hypocalcemia, hypophosphatemia, hypomagnesemia, fever, injection site reaction with intravenous forms, and osteonecrosis of the jaw.[21,62] As with other therapies, the use of bisphosphonates in calciphylaxis has not been supported by randomized controlled trials. While bisphosphonate therapy has likely contributed to favorable outcomes in several patients, Food and Drug Administration (FDA) labeling cautions against its use in patients with chronic renal failure and a glomerular filtration rate of less than 30 mL/min.[73] Nonetheless, 5 out of 6 reported cases of calciphylaxis successfully treated with bisphosphonates described patients on hemodialysis for CKD.[63,65-68] Furthermore, the predominant opinion that bisphosphonates are dialyzable may mitigate concerns about their use in CKD patients on hemodialysis.[73]

Cinacalcet

Cinacalcet is a calcimimetic agent approved for treating secondary hyperparathyroidism in patients with CKD who are on dialysis, as well as for hypercalcemia in parathyroid cancer.[74] Cinacalcet increases the sensitivity of parathyroid cell

calcium-sensing receptors, resulting in suppression of PTH secretion.[52,75,76]

Seven patients with calciphylaxis in the published literature have been treated successfully with cinacalcet.[6,75-79] These patients experienced pain relief within weeks to months, with ulcer resolution taking 2 to 14 months. Treatment with cinacalcet was aimed at reducing serum calcium, phosphate, and PTH levels in dialysis patients with secondary hyperparathyroidism.[80] This raises the question of whether cinacalcet would be effective for calciphylaxis in the absence of hyperparathyroidism. Ackermann et al[41] describe a patient with calciphylaxis, low intact PTH, hypercalcemia, and hyperphosphatemia in whom cinacalcet therapy yielded further decrease in PTH levels and clinical deterioration in the setting of worsening adynamic bone syndrome.[41] In addition, Khalpey et al[81] describe a patient with end-stage renal disease and secondary hyperparathyroidism in whom cinacalcet reduced PTH levels and normalized serum calcium levels, but failed to prevent calciphylaxis.

Two case reports outline response to cinacalcet at different doses in distal versus proximal calciphylaxis.[6,75] Velasco et al[75] describe a patient in whom the resolution of distal leg ulcers required cinacalcet, 60 to 120 mg daily, for 9 months. Mohammed et al[6] successfully treated proximal calciphylaxis lesions using a lower dose of 30 mg daily for 5 months. While more data are required to inform appropriate dosing of cinacalcet for calciphylaxis, clinicians may use these case reports to guide initial therapy.

Potential adverse effects of cinacalcet include nausea, vomiting, hypocalcemia, and adynamic bone syndrome. Cinacalcet is also a significant CP-450 isoenzyme 2D6 inhibitor and therefore interacts with many drugs.[21] Like other therapeutic options, cinacalcet has not been tested in randomized, controlled clinical trials for calciphylaxis treatment. While case reports have been promising, clinicians should be cautious of using cinacalcet in the absence of hyperparathyroidism.

Corticosteroids

Some authors endorse using systemic corticosteroids in calciphylaxis, with the goal of decreasing tissue inflammation.[10,82] Two case reports have documented the successful use of corticosteroids in calciphylaxis.[10,82] However, other reports have implicated corticosteroids in the development of calciphylaxis.[1,3,83] Furthermore, of 5 reports of documented non-uremic calciphylaxis treated with corticosteroids, 4 resulted in death.[14,84-87] In addition, given the high risk of wound infection and sepsis in calciphylaxis, caution is warranted before considering systemic corticosteroids for treatment.

SURGERY

Parathyroidectomy

Parathyroidectomy has long been used in attempts to treat calciphylaxis by suppressing or eliminating serum PTH, amid controversy over outcomes.[10,88] The risks of parathyroidectomy in calciphylaxis patients include wound infection, poor wound healing, sepsis, adynamic bone syndrome, hypocalcemia, and hyperphosphatemia. Several small case series have demonstrated improved survival and wound healing after parathyroidectomy.[89-92] However, other similarly small case series document no survival benefit in patients undergoing parathyroidectomy.[1,89,93,94]

Two recent larger retrospective studies have demonstrated no significant difference in survival between patients with calciphylaxis who underwent parathyroidectomy and those who did not.[1,89] However, these two studies include only 16 and 9 patients who underwent parathyroidectomy.[1,89] Weenig et al[1] found a 38.3% 1-year survival rate in 47 patients who did not receive parathyroidectomy, compared with 33.3% in 16 patients who underwent parathyroidectomy, with no significant difference between the groups. Lal et al[89] demonstrated a 5-month median survival for patients not receiving parathyroidectomy, compared with a 15-month median survival for 9 patients who did, with no significant difference between groups. Notably, 51 of 63 patients (81%) and 22 of 24 patients (92%) from the respective studies died during follow up, most commonly from sepsis.

The lack of large numbers of patients represents a significant limitation in these studies. In addition, patients were not randomized to receive parathyroidectomy; therefore selection bias may also play a role. Lal et al[89] note that while there were no other clinical or laboratory differences between study groups, those patients who underwent parathyroidectomy had higher PTH levels (663.6 ± 87.0 pg/mL vs 83.8 ± 75.6 pg/mL; $P = .04$) and higher phosphate levels (5.0 ± 1.33 mg/dL vs 3.7 ± 0.89 mg/dL; $P = .03$) than patients who did not undergo parathyroidectomy. These factors could have increased mortality risk in the parathyroidectomy group, thereby making it more challenging to note a statistically significant mortality benefit in patients who underwent surgery.

Given the similarity in mechanism by which parathyroidectomy and the newly developed cinacalcet exert their effects (suppression of serum PTH), studies designed to compare the efficacy of these two methodologies in calciphylaxis are needed. On the basis of the few promising reports to date, several

authors suggest that cinacalcet may represent a medical alternative to parathyroidectomy in cases of calciphylaxis with hyperparathyroidism.[6,20,75,77,81,95] Furthermore, as with cinacalcet, the potential role of parathyroidectomy in calciphylaxis occurring in the absence of hyperparathyroidism remains unclear; Kang et al[93] advocate that parathyroidectomy is likely to help in calciphylaxis only if patients have concurrent severe hyperparathyroidism.[89]

WOUND MANAGEMENT

Hyperbaric oxygen therapy

Hyperbaric oxygen (HBO) therapy has been used for more than a century in various medical indications.[96] Today, HBO is used to treat decompression sickness and carbon monoxide poisoning and has also garnered attention for wound healing.[59,97,98] To date, 46 cases of calciphylaxis treated with HBO have been published, with 34 noting success.[15,99-108] These patients were treated by 10 different groups of authors, with the largest case series including 12 patients. Notably, adjunctive therapies for calciphylaxis were also used in every patient receiving HBO.

HBO is purported to exert beneficial effects in calciphylaxis through multiple mechanisms, including stimulation of fibroblast proliferation and conversion to myofibroblasts instrumental in wound contraction, stimulation of neoangiogenesis, promotion of arteriolar constriction to prevent edema and tissue reperfusion injury, prevention of wound infection by direct toxicity against *Clostridia* species, bacteriostatic activity against *Escherichia* and *Pseudomonas* species, and support of neutrophils in generating reactive oxygen species.[9,59]

Potential adverse effects of HBO include claustrophobia, myopia, and barotrauma to ears, lungs, and sinuses; however, side effects tend to be mild and reversible.[59] While the potential adverse effects of HBO may be tolerable, access may be challenging and costly. With a typical cost of $300 to $400 per 90-minute session, and 20 to 40 sessions recommended for wound treatment, the cost of HBO may range from $9,000 to $16,000 or more.[97,109,110] Furthermore, its use may not be reimbursed by Medicare and Medicaid, which currently cover HBO for only limited indications.[110,111]

Surgical debridement and atraumatic methods, including sterile maggot therapy

There is a lack of evidence-based literature for wound care in calciphylaxis. Some authors advocate aggressive surgical debridement of devitalized tissue for infection prevention,[15,52] whereas others promote enzymatic agents, hydrocolloid dressings, or other atraumatic debridement methods to prevent skin trauma that can lead to additional calciphylaxis lesions.[2,3,12,20] Some advise against the debridement of dry, uninfected necrotic wounds in ischemic disease, arguing that intact eschar may serve as a barrier against infection; however, clinical evidence supporting this approach in calciphylaxis is lacking.[112] Overall, no consensus on wound management exists.[15]

Two studies associate surgical debridement in calciphylaxis with significant improvements in survival rates.[1,89] Conclusions inferred from these retrospective studies should be tempered by their lack of standardized, controlled indications for wound debridement and for surgical technique employed during debridement. Measurement of transcutaneous oxygen tension has been shown to be effective in identifying areas of cutaneous ischemia in calciphylaxis; such measurement has the potential to be useful in developing a consistent approach to surgical debridement of devitalized tissue.[3,113]

Tittelbach, Graefe, and Wollina[114] employed a minimally traumatic approach to wound debridement in calciphylaxis by applying sterile maggots after a patient could not tolerate mechanical debridement because of pain. The clinicians used larvae of the greenbottle fly (*Lucilia sericata*) and reported complete debridement and stimulation of granulation tissue after 3 treatments lasting 3 days each. While this treatment methodology demonstrated benefit, its use in calciphylaxis has been reported in only one patient.

CONCLUSION

Calciphylaxis is a condition with high morbidity and mortality, which warrants a multidisciplinary approach. No randomized controlled trials dictate therapy in this rare disease. Clinicians must remain vigilant about preventing sepsis and treating pain in addition to considering the therapeutic strategies detailed in this article.

In patients with chronic renal failure who develop calciphylaxis, therapy should include attempts to decrease the serum calcium-phosphate product, to substitute calcium-containing phosphate binders with calcium-free phosphate binders, and to use normocalcic dialysate. Bisphosphonates or cinacalcet may also be helpful, with care being taken for appropriate patient selection. Because of the increased potential for infection, sepsis, and anesthesia-related hypotension exacerbating already compromised microvascular autoregulation in calciphylaxis, clinicians should consider cinacalcet as an alternative to parathyroidectomy for cases with associated hyperparathyroidism.[6,20,75,77,81,95] Wound care objectives should include pain control,

avoidance of trauma, and the prevention of infection. Emerging evidence indicates that intravenous STS should be strongly considered as well.

Combination approaches to the management of calciphylaxis are often required. The traditional approach utilized at the authors' institution includes a combination of gentle reduction of the calcium-phosphate product as warranted, wound care chiefly aimed at the prevention of infection with the avoidance of unnecessary trauma, and a trial of intravenous sodium thiosulfate.

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