CLINICAL MANAGEMENT extra

Calciphylaxis: Diagnosis, Pathogenesis, and Treatment

CME
1 AMA PRA
Category 1 Credit™

CE
ANCC
1.5 Contact Hours

Rx
0.5 Pharmacology Contact Hour

John J. Chang, MD • Assistant Professor • Department of Internal Medicine • Yale School of Medicine, New Haven, Connecticut

The author, faculty, staff, and planners, including spouses/partners (if any), in any position to control the content of this CME/CNE activity have disclosed that they have no financial relationships with, or financial interests in, any commercial companies relevant to this educational activity.

To earn CME credit, you must read the CME article and complete the quiz online, answering at least 13 of the 18 questions correctly.

This continuing educational activity will expire for physicians on April 30, 2021, and for nurses on March 5, 2021.

All tests are now online only; take the test at http://cme.lww.com for physicians and www.nursingcenter.com for nurses. Complete CE/CME information is on the last page of this article.

GENERAL PURPOSE:

To provide information on the pathogenesis, clinical features, diagnosis, and treatment of calciphylaxis.

TARGET AUDIENCE:

This continuing education activity is intended for physicians, physician assistants, nurse practitioners, and nurses with an interest in skin and wound care.

LEARNING OBJECTIVES/OUTCOMES:

After participating in this educational activity, the participant should be better able to:

1. Recognize the pathogenesis and clinical features of and risk factors for calciphylaxis.

2. Explain the diagnosis and management of a patient with calciphylaxis.

ABSTRACT

Calciphylaxis is a cutaneous ischemic infarct caused by total occlusion of blood vessels initiated by vascular calcification. Until recently, treatments have been limited to controlling its risk factors and optimizing wound care. However, recent advances in clinical understanding of the mechanism of calciphylaxis have identified promising potential therapeutic targets. This article is a narrative review summarizing the clinical features, diagnosis, pathogenesis, and treatment of calciphylaxis.

KEYWORDS: calcification, calciphylaxis, cutaneous disease, end-stage renal disease, infection, renal failure, skin disease, wound care

ADV SKIN WOUND CARE 2019;32:205–15.

INTRODUCTION

Calciphylaxis is a cutaneous ischemic infarct caused by occlusion of blood vessels in the subcutaneous fat and dermis. Severe pain and propensity for infections make calciphylaxis highly debilitating with an annual mortality of 40% to 80%.[1]

"Calciphylaxis" is derived from "calci" meaning calcification and "phylaxis," meaning protection, and literally means protection by calcification. The term was coined by Dr Seyle in 1961 to describe the formation of a calcium shell on rat skin.[2] In a high calcium and phosphate milieu generated by ingestion of parathyroid hormone (PTH) or vitamin D, a minor skin trauma by iron dextran injection or hair removal precipitated a massive calcium deposition. Over the next 3 weeks, the calcified skin detached itself from the underlying skin. By the fourth week, the rat crept out of its hard calcium "shell" with completely new and normal skin. Dr Seyle postulated that the rat skin developed a calcium shell to protect it from further injuries, hence the term "calciphylaxis."[2]

Later, calcifying skin lesions that developed in humans with renal failure were named calciphylaxis because of their similarities to the calcified rat skin.[3,4] Besides sharing the histologic hallmark of calcification, both human and rat calciphylaxis developed under the seemingly same metabolic conditions of high PTH and phosphate levels.

As more cases of calciphylaxis in humans were described, important differences between rat and human calciphylaxis were noted.[5] While calcification develops outside the vessels in both rats and humans, only in humans does it also develop within the vessel walls. In rats, the calcified skin is replaced with a new skin, but no such replacement occurs in humans; accordingly, it is life-threatening to humans.

The last two decades have seen significant advances in clinical understanding of how calciphylaxis develops: in humans, it appears to be the skin equivalent of a myocardial infarction, not a protective response. As a result, patients now have a new paradigm for its treatment with promising potential therapeutic targets. This article is a narrative review summarizing the clinical features, diagnosis, pathogenesis, and treatment of calciphylaxis.

METHODS

Information for this review was collected from textbooks, a review of references, and PubMed searches. The MeSH term "calciphylaxis" was used to identify 835 articles in English published between 1960 and 2018. Of these, 548 articles were categorized under the subheading "etiology," 262 articles under "diagnosis" or "pathology," and 333 articles under "therapy." There were 131 review articles and 3 clinical trials. All articles were selected based on their relevance for diagnosis, pathogenesis, and treatment of calciphylaxis. This review contains 50 key references.

KEY CLINICAL FEATURES

Calciphylaxis is primarily a disease of renal failure; a majority of patients are nearing or on dialysis. Calciphylaxis that develops in end-stage renal disease (ESRD) patients is classified as uremic calciphylaxis. Estimates for the annual incidence of uremic calciphylaxis vary from as high as 4% in early and single-center studies[1,6] and as low as 0.04% in Germany and 0.35% in the US in more recent and national studies.[7,8] The actual incidence is probably higher than the most recent estimates; some cases were likely missed from misdiagnosis and underreporting. Despite the relatively low incidence, calciphylaxis will continue to be encountered in clinical practice for the foreseeable future, because of the rising number of ESRD patients in the last 25 years: in 2015, nearly half a million patients were on hemodialysis and peritoneal dialysis in the US.[9]

Calciphylaxis in patients with preserved renal function is known as nonuremic calciphylaxis. Its incidence is unknown but is likely much lower than that of uremic calciphylaxis. As of 2016, only 116 cases were reported in the literature.[10]

The risk factors for calciphylaxis fall into four major categories (Table 1). The strongest risk factor is renal failure, with a majority of cases of calciphylaxis developing in dialysis or renal transplant patients. Second, derangements in calcium and phosphate homeostasis, including hyperphosphatemia, hypercalcemia, and hyper- and hypoparathyroidism, predispose to the development of calciphylaxis.[8] Third, vitamin K deficiency greatly increases risk because vitamin K activates a potent inhibitor of calcification, as described below.[11] At the time of presentation, 40% to 50% of calciphylaxis patients are taking a vitamin K antagonist such as warfarin.[7] Finally, obesity, diabetes mellitus, and female sex are risk factors.[1,12]

Table 1.
RISK FACTORS FOR CALCIPHYLAXIS

End-stage renal disease
Peritoneal dialysis > hemodialysis > renal transplant
Derangements in calcium and phosphate homeostasis
Hyperphosphatemia
Hypercalcemia
Hyper- and hypoparathyroidism
Vitamin D
Vitamin K deficiency
Warfarin
Comorbid conditions and demographic factors
Obesity
Rapid weight loss
Diabetes mellitus
Female sex

Severe pain is a prominent and nearly universal feature of calciphylaxis.[12] Pain, which is believed to be both ischemic and neuropathic in origin, is often out of proportion to the clinically evident skin injuries and can even precede the appearance of skin lesions.[13,14] A high dose of analgesics is required, but pain may be refractory. A majority of patients end up confined to a wheelchair or to bed because of calciphylaxis.[12]

Calciphylaxis lesions include livedo reticularis, plaques, nodules, and ulcers (Figure 1).[14] Livedo reticularis, a lesion that presents early in the disease process, is a net-like (or reticulated) violaceous or livid skin discoloration. The unique pattern of discoloration results from the altered vascular supply to the skin. Each cutaneous arteriole, which originates deep in the dermis, supplies a cone of skin with a 1- to 3-cm circular base on the surface and its apex in the deep dermis.[15,16] At the boundaries of each cone are watershed areas with relatively diminished blood flow, which are vulnerable to ischemia. When subcutaneous and dermal arteries become occluded, ischemia develops preferentially in the watershed areas, while the central areas are spared, giving rise to a pattern of discoloration.

Plaques or nodules are the most common presenting lesions; a plaque was the presenting lesion in 80% of patients in one study.[1]

Plaques may be confused with cellulitis because they are both red, warm, and tender. The induration unique to calciphylaxis can help differentiate it from cellulitis. One-third of plaques progress to ulcers. Leg ulcers in calciphylaxis are almost always bilateral; there may be one large confluent ulcer or a crop of multiple small ulcers. They often become superinfected.

Calciphylaxis preferentially involves the adipose tissues; the most frequently affected sites are the thighs and abdomen.[8] Calciphylaxis also tends to appear on sites of repeated skin trauma, for example, the risk of calciphylaxis on the abdomen and/or thighs progressively rises with the increasing number of daily insulin injections.[8]

Calciphylaxis lesions typically appear after patients have been on dialysis for a few years. In the largest retrospective review of more than 1,000 dialysis patients with calciphylaxis, the median time between dialysis initiation and development of calciphylaxis was 2.5 years.[8]

PATHOPHYSIOLOGY

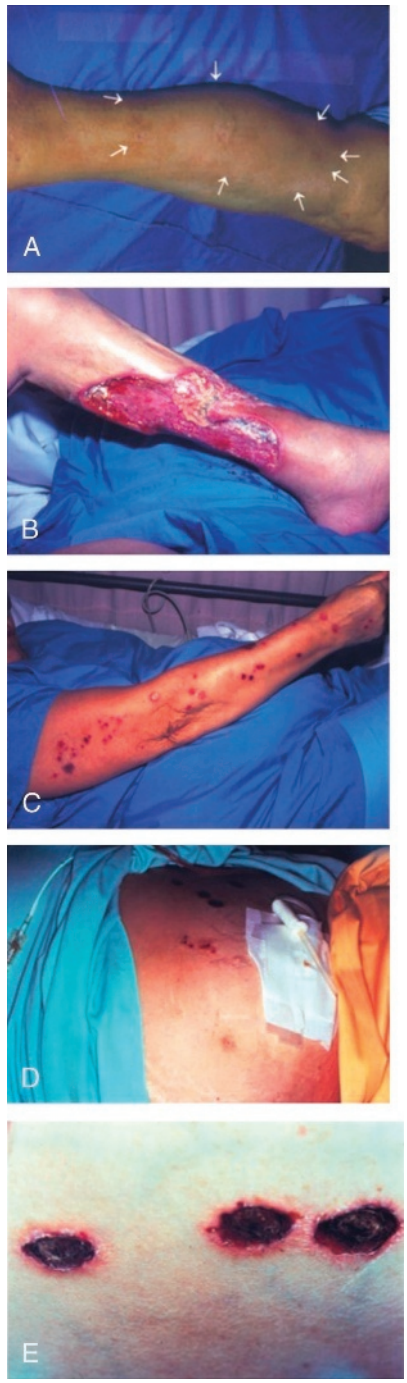
Calciphylaxis is an occlusive disease of cutaneous blood vessels (Figure 2A).[5] Their lumens undergo progressive narrowing first by calcification within the media layer of vessel walls (also known as medial calcification) and proliferation of endothelial cells and fibrosis underneath the intima (also known as subintimal fibroplasia). When thrombosis later develops in the vessel lumen, ischemic injuries develop.

On this march toward complete occlusion, vascular calcification is the inciting and central event. (In the rest of this review, vascular calcification will be used to refer to medial calcification to avoid confusion with the more common use of *medial* as referring to the center of the body.) Vascular calcification is actually an ectopic bone formation in the vessel walls by vascular smooth muscle cells. In response to hyperphosphatemia, hypercalcemia, and hyperglycemia, vascular smooth muscle cells transform into osteoblast-like cells able to produce and deposit hydroxyapatite crystals, building blocks of bone.[17,18] In addition, adipocytes exposed to high phosphate can transform vascular smooth muscle cells to calcify in vitro, providing a possible explanation for the propensity of calciphylaxis in adipose tissues.[19] Vascular endothelial growth factor A and leptin released from adipocytes appear to be mediators. Notably, the conditions that transform vascular smooth cells are the very risk factors for calciphylaxis. Accordingly, calciphylaxis risk factors confer their risk by promoting transformation of vascular smooth muscle cells into osteoblast-like cells.

The most common clinical scenario that gives rise to calciphylaxis is a lack of molecular calcification inhibitors in the vessel wall.[20,21] This deficiency is most commonly attributable to a lack of vitamin K (Figure 2B). Vitamin K activates a potent inhibitor of calcification called matrix Gla protein (MGP), secreted by vascular smooth muscle cells and endothelial cells.[17,21]

There are two common reasons for vitamin K deficiency in ESRD patients. First, intake of leafy green vegetables and dairy products, both rich in vitamin K, is restricted in ESRD patients to limit potassium and sodium intake.[22] Second, a vitamin K antagonist like warfarin inhibits the recycling of vitamin K. Nearly 40% to 50% of ESRD patients with calciphylaxis are taking warfarin at the time of diagnosis.[7]

Figure 1.
CALCIPHYLAXIS LESIONS



A, Calf plaques (borders outlined by arrows). Small plaques often become confluent and may simulate cellulitis because of erythema on the skin. B, Gross ulceration in the same patient 3 months later. The black eschar has been surgically debrided. Small ulcers on an arm (C) and (D) on an abdomen; E, close-up view. Reprinted from Fine A, Zacharias J. Calciphylaxis is usually non-ulcerating: risk factors, outcome and therapy. Kidney Int 2002;61(6):2210-7.

Thrombosis is the final event that leads to complete vessel occlusion. The propensity for thrombosis in calciphylaxis is explained by the high prevalence of congenital and acquired hypercoagulable conditions in calciphylaxis patients. In 55 patients with calciphylaxis, 36 patients (65%) had at least one hypercoagulable condition, with 11 (20%) having two conditions.[23] Among the most common conditions were antithrombin deficiency, lupus anticoagulants, and protein C and S deficiency. In a case-control study of 38 calciphylaxis patients, lupus anticoagulants, protein C deficiency, and the presence of two hypercoagulable conditions were associated with the increased risk of calciphylaxis.[24]

In summary, calciphylaxis develops because the peculiar biochemical environment in ESRD of abnormal phosphate, calcium, and PTH and vitamin K deficiency causes the skin vessels to calcify. Because a majority of calciphylaxis patients have preexisting hypercoagulable conditions, thrombosis readily occurs in the calcified vessels (Figure 3).

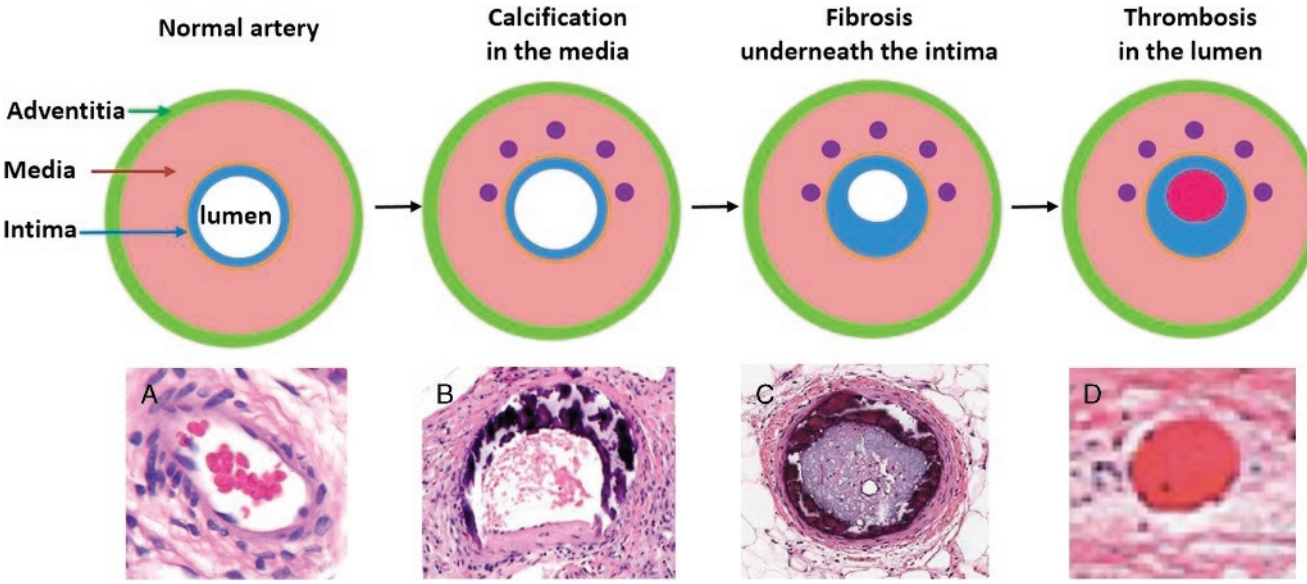
DIAGNOSIS

Diagnosis can be made on clinical grounds alone when a patient with ESRD presents with indurated tender plaques or ulcers on the abdomen and/or legs.[14] However, skin biopsy may be necessary to differentiate calciphylaxis from its mimics (eg, pyoderma gangrenosum, Martorell hypertensive ischemic leg ulcer, cholesterol emboli, etc; Table 2), especially when calciphylaxis presents in early stages with clinically nondescript lesions such as a small papule and erosion.[25,26] Skin biopsy is also recommended to help diagnose nonuremic calciphylaxis.[14]

In contrast, skin biopsy is not always indicated in uremic calciphylaxis because the likelihood of calciphylaxis is much higher when an ESRD patient presents with characteristic skin lesions, as compared with patients with preserved renal function. No consensus exists on the role of a skin biopsy in diagnosing uremic calciphylaxis. When 12 European experts on calciphylaxis were asked, five (42%) reported that a skin biopsy is a prerequisite for diagnosis, while four (33%) did not, and three (25%) were undecided.[27] The results of this survey reflect the current practice pattern in the US. In a study of more than 1,000 patients with calciphylaxis, 55% were diagnosed with a skin biopsy, and the remaining 45% were diagnosed clinically.[8] The possibility of nondiagnostic biopsies (resulting in a need for repeat biopsies) and the risk of complications are the reasons why biopsies are not universally pursued.

A punch biopsy with a double trephine technique is the preferred biopsy method.[14,28] An 8-mm circular core of superficial tissue is first obtained using an 8-mm punch tool. Then, a 4- to 6-mm punch tool is inserted within the center of the 8-mm defect to obtain the deep subcutaneous fat. A single punch biopsy should be avoided because the deep subcutaneous fat where pathologic features of calciphylaxis are most frequently found may not be sampled. An excisional biopsy should also be avoided

Figure 2.
HISTOLOGIC PROGRESSION OF CALCIPHYLAXIS



Calciphylaxis is an occlusive disease of cutaneous blood vessels. Their lumens undergo progressive narrowing first by calcification in the media and fibrosis underneath the intima. When thrombosis later develops in the vessel lumen, ischemic injuries develop. Images, left to right: A, Courtesy of Shawn Cowper, MD, Yale Medical School; B, reprinted from Nigwekar SU, Kroshinsky D, Nazarian RM, et al. Calciphylaxis: risk factors, diagnosis, and treatment. Am J Kidney Dis. 2015;66(1):133-146. C, D, reprinted from Weenig RH, Sewell LD, Davis MD, McCarthy JT, Pittelkow MR. Calciphylaxis: natural history, risk factor analysis, and outcome. J Am Acad Dermatol 2007;56:569-79.

because of the potential for ulceration, necrosis, and bleeding.[1,29] The biopsy should be taken from the margin of the lesion, avoiding the center of the lesion or the necrotic area where nonspecific necrotic tissue is more likely to be found.[1,29]

Bone scan may prove to be a reliable, noninvasive diagnostic test for calciphylaxis, especially when biopsy findings are nondiagnostic or when a biopsy cannot be performed. The bone scan is positive when the tracer technetium 99m-labeled medronic acid binds to hydroxyapatite crystals at the calcified areas in the dermis and subcutaneous fat. In one study, bone scan yielded a sensitivity of 87% and a specificity of 97%.[30] False-negatives resulted only from ulcers, which had no tracer uptake either because the occluded vessels prevented tracer delivery or because the calcified tissue was sloughed off. Mammogram and X-rays may also show calcification but have a lower sensitivity.[1,31] Their specificities are unknown.

Laboratory evaluation is diagnostically unhelpful. While hyperphosphatemia, hypercalcemia, and hypo/hyperparathyroidism are risk factors for calciphylaxis, many patients do not present with abnormal values. As a corollary, normal and even low calcium and phosphate levels do not rule out calciphylaxis (Figure 4).

PREVENTION AND TREATMENT

Treatment of calciphylaxis requires a multidisciplinary approach involving nephrologists, dermatologists, plastic surgeons, dietitians, and wound care specialists.[8] Because vascular calcification is the critical event that ultimately leads to vascular occlusion, a logical treatment objective is to stop the vascular calcification. In fact, many of the conventional treatment options are agents to stop vascular calcification. Decalcification of the calcified vessels to restore blood flow is a second treatment objective. The final objective is wound care and pain management.

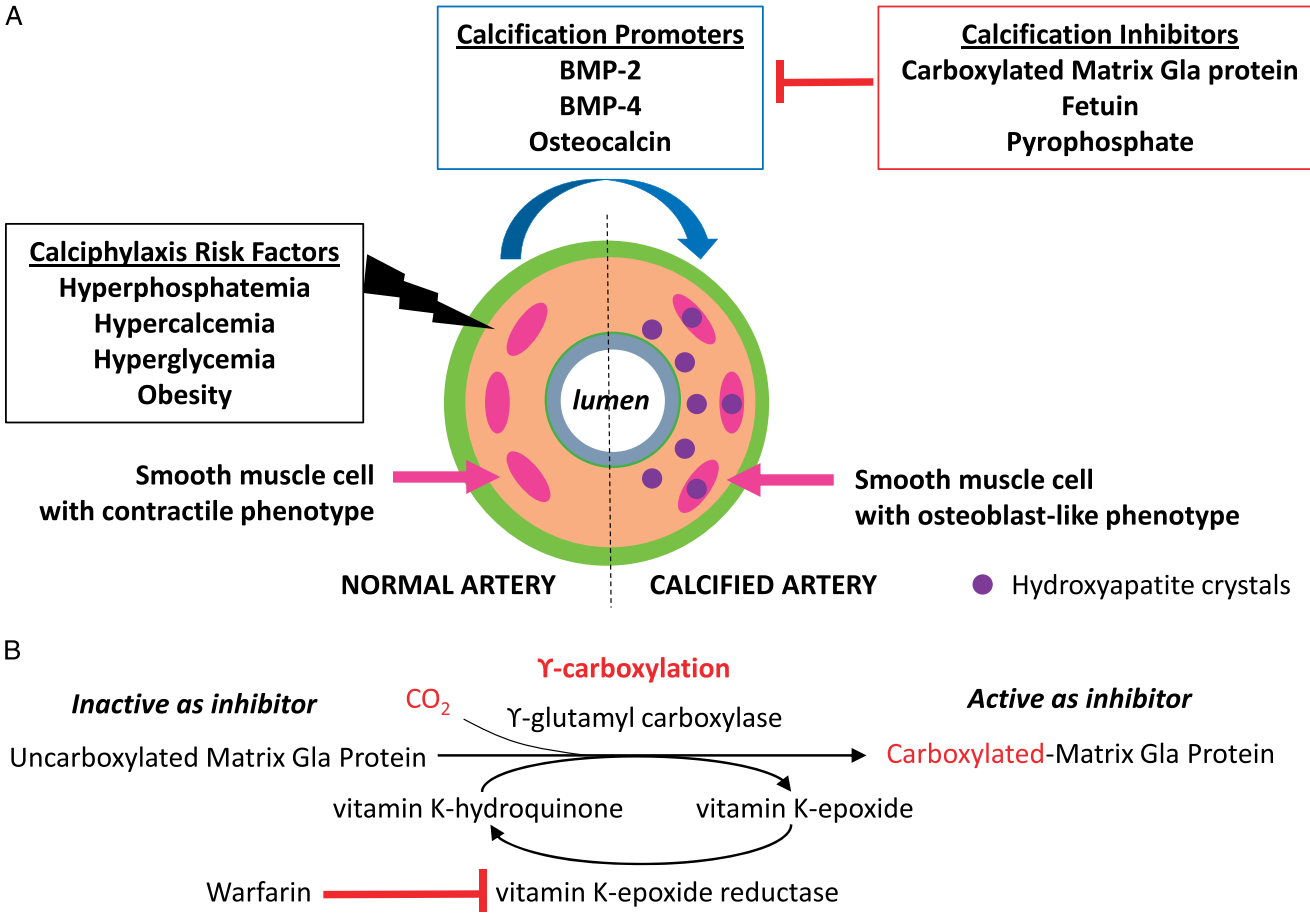
It should be noted that the treatment recommendations discussed in this section lack robust data: the data come from observational retrospective studies with small sample sizes, surveys of clinicians, case series, and expert opinions.[32] Clearly, more rigorous investigations are needed, and in fact some are underway (as will be discussed). Considering the debilitating and lethal nature of calciphylaxis, however, the lack of robust data should not dissuade the adoption of treatment options after a frank discussion with the patient about the risks, benefits, and limitations of each treatment option.

Strategies to Stop Vascular Calcification

Countermeasures to stop vascular calcification aim to either ameliorate or eliminate each of the risk factors for calciphylaxis (Table 3).

Hyperphosphatemia is treated by increasing phosphate removal and decreasing phosphate intake. Hemodialysis, which is the only route of phosphate elimination for patients on hemodialysis, may need to be increased to four to five times a week to achieve adequate phosphate removal.[33] Avoiding foods rich

Figure 3.
PATHOGENESIS OF CALCIPHYLAXIS



A, Medial calcification is an ectopic bone formation in the vessel walls by vascular smooth muscle cells. In response to hyperphosphatemia, hypercalcemia, and hyperglycemia, vascular smooth muscle cells transform into osteoblast-like cells able to produce and deposit hydroxyapatite crystals. In addition, vascular endothelial growth factor A and leptin released from adipocytes exposed to high phosphate can transform vascular smooth muscle cells. Bone morphogenetic proteins 2 and 4 and osteocalcin promote calcification. The balance of calcification promoters and inhibitors determines whether calcification develops. B, A lack of matrix Gla protein (MGP), a potent calcification inhibitor in the vessel wall, has been implicated in the development of calciphylaxis. This deficiency is in turn attributable to vitamin K deficiency. To be as active as calcification inhibitors, MGPs require addition of carboxyl groups in a vitamin K-dependent reaction called gamma carboxylation. In the blood and skin lesions of patients with calciphylaxis, a majority of MGPs are not carboxylated and thus remain inactivated. This is in contrast to the preponderance of carboxylated MGPs in patients without calciphylaxis. The relative lack of carboxylated MGPs leads to unopposed vascular calcification and calciphylaxis. During gamma carboxylation, vitamin K is oxidized. To participate in another round of gamma carboxylation, vitamin K needs to be recycled back to a hydroquinone. Warfarin prevents vitamin K recycling by inhibiting vitamin K epoxide reductase. Abbreviation: BMP, bone morphogenetic protein.

in phosphate, such as colas and processed foods, and consistent use of oral phosphate binders to reduce absorption of dietary phosphate are crucial. Target blood phosphate level is around 3 mg/dL.

Hypercalcemia is treated by increasing calcium removal by dialysis and reducing calcium intake.[33] Calcium-based phosphate binders such as calcium acetate should be avoided because the absorption of calcium can cause hypercalcemia.[33] The goal blood calcium level is around 8 mg/dL.

The ideal PTH level in calciphylaxis is not known, but both extremely high and low values should be avoided.[8] Levels of PTH in blood can be lowered by suppressing its secretion by cinacalcet, and in refractory cases by parathyroidectomy. Vitamin D supplements should be stopped.[8]

Warfarin should be discontinued in patients with calciphylaxis, and the need for continuing anticoagulation with an alternative anticoagulant should be carefully assessed.[8,29] Stroke prevention in atrial fibrillation is the most common indication for warfarin in dialysis patients. However, no data exist to support anticoagulant use for this indication, and therefore anticoagulation can be stopped altogether.[34] Less commonly, clinical scenarios do arise, such as treatment of pulmonary embolism and prevention of clots on

Table 2.
DIFFERENTIAL DIAGNOSES OF CALCIPHYLAXIS

Skin Condition *Typical Skin Lesions*	Pathogenesis	Distinguishing Features
Calciphylaxis[a] *Livedo reticularis* *Plaque* *Ulcer*	Occlusion of dermal and subcutaneous arteries initiated by calcification and fibrosis of blood vessel walls and later completed by intraluminal thrombosis	Painful plaques and ulcers in adipose tissues of patient with end-stage renal disease, chronic warfarin use, and hyperphosphatemia
Martorell hypertensive ischemic leg ulcer *Ulcer* *Livedo reticularis*	Atherosclerosis of the peripheral arteries	Involvement of the lateral-dorsal aspect of the calf and the Achilles tendon, often normal renal function, and often palpable pulse with normal ABI unless concurrent peripheral artery disease
Peripheral artery disease *Cyanosis* *Ulcer*	Atherosclerosis of the peripheral arteries	Punched-out wound margins, claudication, weak or absent pulse, and abnormal ABI
Pyoderma gangrenosum *Ulcer*	Neutrophilic dermatosis of unknown etiology	*Over* 50% have an associated systemic disease (inflammatory bowel disease, arthritis, hematologic disorder) and pathergy[b]
Purpura fulminans *Purpura* *Ulcer*	Disseminated intravascular coagulation precipitated by a severe infection	Severe infection
Warfarin-induced necrosis *Purpura* *Ulcers*	Transient hypercoagulability early in warfarin therapy from depletion of protein C & S, endogenous anticoagulants	Recent warfarin initiation
Cholesterol emboli *Livedo reticularis* *Blue toe*	Arteriole occlusion by cholesterol emboli from atherosclerotic plaques	Recent vascular procedure (eg, cardiac catheterization)
Heparin-induced thrombocytopenia *Purpura* *Ulcer*	Platelet activation by antibodies against a complex of heparin of platelet factor 4 found on the platelet surface	Recent heparin exposure, thrombocytopenia, and new venous and arterial thrombosis
Nephrogenic systemic fibrosis *Plaque*	Excess dermal collagen deposition caused by gadolinium accumulating in renal failure	History of MRI with gadolinium
Vasculitis *Livedo reticularis* *Purpura* *Ulcer*	Inflammation in the blood vessel walls	Extracutaneous symptoms (fever, abdominal pain, melena, dyspnea, hemoptysis, neuropathy, etc)

[a]Calciphylaxis is distinguished from its mimics by a triad of histologic findings in the blood vessels of the dermis and subcutaneous fat: (1) medial calcification; (2) subintimal fibroplasia; and (3) intraluminal thrombosis.
[b]Induction or exacerbation of a skin lesion after a minor trauma, but not specific to pyoderma gangrenosum
Abbreviation: ABI, ankle-brachial index.

mechanical heart valves, when anticoagulation cannot be stopped. In these situations, apixaban, a direct factor Xa inhibitor, has been used.[35,36] A note of caution for bleeding complications needs to be issued, because there are only limited safety profile data for apixaban in patients with advanced chronic kidney disease.

The transition to hemodialysis should be considered for peritoneal dialysis patients who develop calciphylaxis; the benefit is attributed to better phosphate and calcium control.[8] In addition, hemodialysis allows the concurrent administration of IV sodium thiosulfate during hemodialysis sessions (see below).

Strategies to Decalcify Calcified Vessels

Two agents have been shown to promote blood vessel decalcification.

Figure 4.
CALCIPHYLAXIS HISTOLOGY

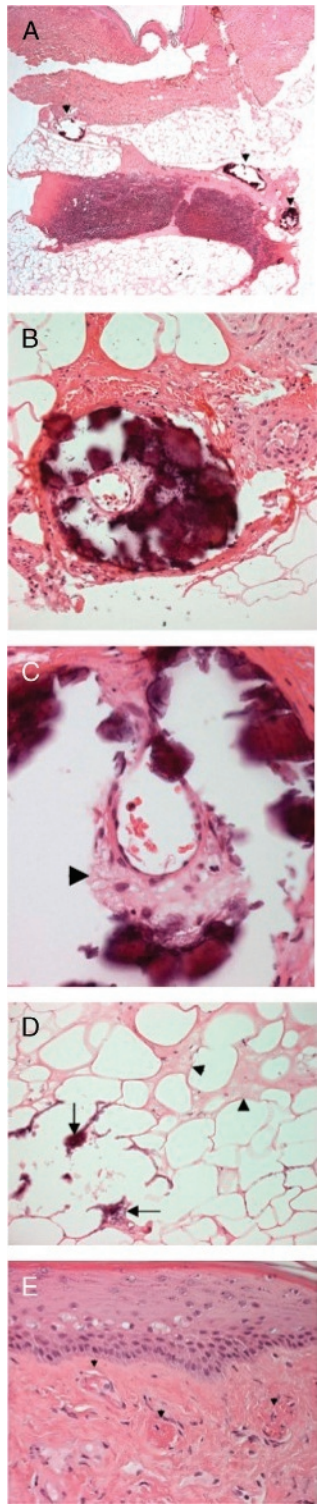


Figure 4.
CALCIPHYLAXIS HISTOLOGY, CONTINUED

Original magnification ×25 (A), ×200 (B and D), ×400 (C and E). The characteristic histologic findings of calciphylaxis include vessel wall calcification (arrowheads in inset A with enlarged view in inset B), subintimal fibroplasia (arrowhead in inset C), and intraluminal thrombosis (arrowheads in inset E) in the blood vessels of the dermis and subcutaneous fat. Calcifications may also be found outside the vessels, in the dermal collagen, around the eccrine sweat glands, in and arounds the adipocytes (arrows in inset D), and in the septa. Alizarin or von Kossa staining are special stains for calcium and can improve the detection of calcifications. Vascular calcifications may be seen in several other conditions including atherosclerotic peripheral vascular disease, Mönckeberg sclerosis, and calcinosis cutis. However, stippled calcification, calcification of capillaries, and calcification in the internal elastic lamina and around the eccrine glands strongly point to calciphylaxis. Inflammation and necrosis (arrowheads in inset D), a consequence of ischemia, are observed in the dermis and subcutaneous fat. Reprinted from Weenig RH et al. Calciphylaxis: natural history, risk factor analysis, and outcome. J Am Acad Dermatol 2007;56:569–79

Sodium thiosulfate. Since its first report of successful use in 2004, sodium thiosulfate is now considered by most to be a standard therapy for calciphylaxis.[8,37] Multiple mechanisms have been proposed to account for its therapeutic benefits.[38,39] As a calcium chelator, sodium thiosulfate has been shown to decalcify the calcified vessel walls.[40] Thiosulfate binds the calcium ions, and the resulting complexes of thiosulfate and calcium, which are highly water-soluble, are eliminated in urine or by dialysis. As an antioxidant, sodium thiosulfate may neutralize reactive oxygen species that promote inflammation, thrombosis, and vasoconstriction.

Intravenous delivery during the last hour of a hemodialysis session is standard. The dose is weight based: 25 g for weight greater than 60 kg and 12.5 g for weight less than 60 kg. A minimum duration of treatment is 3 months. Typically, the total duration of treatment is about 6 months or until the lesions completely heal.[8]

Sodium thiosulfate has been successfully used by directly injecting it around the border of and into the center of the lesion.[41] The injection is useful for patients with limited intravenous access. The dose is 0.25 to 0.75 g (or 1–;3 mL of the 250 mg/mL sodium thiosulfate solution). This therapy is well tolerated. While common, nausea and vomiting are self-limited in most patients and only rarely necessitate discontinuation. Metabolic acidosis is common but is clinically insignificant.[42]

Sodium thiosulfate appears to be beneficial in a majority of patients with calciphylaxis. The best available data on its efficacy come from surveys of clinicians at US hemodialysis centers.[42] Of the 53 patients whose clinicians returned the surveys, nearly three-quarters had either a complete (26%) or a partial (47%) response. Only three patients (6%) showed no response. The response was unknown in 11 (21%) because of incomplete surveys. To more definitively answer the question of its efficacy, randomized clinical trials are underway, comparing sodium thiosulfate to placebo (Current Controlled Trials no. ISRCTN73380053 and ClinicalTrials.gov no. NCT03150420).

Table 3.
CALCIPHYLAXIS TREATMENT

Strategies to stop calcification of blood vessels	
Correct hyperphosphatemia	▪ More and longer dialysis sessions (4-5 times/wk)
	▪ Dietary phosphate restriction: avoid colas and processed foods; seek nutrition consult
	▪ Non-Ca^{++} phosphate binder
Correct hypercalcemia	▪ Reduce Ca^{++} concentration in dialysis bath to 1.5 or 2 mEq/L; avoid 2.5 mEq/L
	▪ Stop Ca^{++} based phosphate binder (Ca^{++} acetate)
Correct hyperparathyroidism	▪ Cinacalcet (medical parathyroidectomy)
	▪ Surgical parathyroidectomy in medically refractory cases
Stop vitamin D	▪ Eg, calcitriol
Stop warfarin	▪ Evaluate need for alternate anticoagulant
	▪ No data to justify anticoagulation for stroke prevention in atrial fibrillation in dialysis patients
	▪ Apixaban 2.5 mg bid in pulmonary embolism, deep vein thrombosis, mechanical valve (limited safety data)
Convert to hemodialysis from peritoneal dialysis	
Strategies to promote decalcification of blood vessels	
Sodium thiosulfate	▪ Route and dose
	-Intravenous (standard): 25 gm if weight > 60 kg; 12.5 gm if weight < 60 kg; infusion in the last hour of dialysis
	-Subcutaneous (nonstandard): 0.25 to 0.75 gm (1 to 3 mL of 250 mg/mL); at the periphery and center of the lesion
	▪ Duration of IV infusion: minimum of 2-3 mos; typical total duration of 6 mos or until lesions completely heal
Vitamin K	▪ Investigational
	▪ Route and dose: 10 mg per os three times a week (normal daily vitamin K intake: 0.10 – 0.15 mg)
Wound care and pain control	
Debridement	▪ Surgical debridement for infected and wounds with exudates
	▪ Nonsurgical debridement for noninfected and dry wounds
Hyperbaric oxygen therapy	▪ Delivery of 100% oxygen at 2.5 times the atmospheric pressure in a sealed chamber for 90 min
	▪ Aim for 20–30 sessions (optimal number unknown)
	▪ Reserved for refractory wounds
Pain control	▪ Fentanyl and methadone preferred in renal failure. Avoid morphine and hydromorphone because accumulating active metabolite can cause respiratory depression.

Sodium thiosulfate also appears to confer a mortality benefit. One-year mortality for calciphylaxis before the advent of sodium thiosulfate was estimated at around 55%.[43] In the study that assessed clinical response to sodium thiosulfate by surveys, 1-year mortality was lower, at 35%.[42]

Vitamin K. The discovery that vitamin K deficiency prevents MGP activation and consequently promotes vascular calcification has spurred investigations of vitamin K as a decalcifying agent. Vitamin K retarded the progression of calcification in the coronary arteries and aortic valves in selected studies.[44–46] Vitamin K has also successfully treated calciphylaxis in a single patient.[47]

A proof-of-concept study for vitamin K as therapy for calciphylaxis is ongoing (ClinicalTrials.gov no. 02278692). This trial will randomize 20 patients with calciphylaxis to vitamin K 10 mg orally three times a week for 12 weeks versus placebo. Notably, the treatment dose is approximately 30 times higher the normal dietary intake (0.10–0.15 mg/d). The primary outcome is a change in the carboxylation status of MGP. The secondary outcomes are change in pain levels and the size of lesions.

Wound Care and Pain Management

Optimization of wound healing entails a three-pronged approach with nutrition support, meticulous wound bed management, and possibly oxygenation augmentation.

Wound bed management focuses on moisture control with appropriate dressings, removal of devitalized tissue, and prevention and treatment of infection. Surgical debridement should be strongly considered for infected wounds (to prevent systemic infection) and for large wounds with exudate.[8] Surgical debridement has been associated with survival benefit in a few small retrospective studies.[12,48] However, because the patient selection was not controlled, improved survival might have resulted from a selection of patients with more limited disease or fewer comorbid conditions. It should be remembered that severe pain in the wound bed makes any debridement, let alone surgical debridement, a challenge to perform. Severe hypoxia in the wound bed means that any surgical debridement runs the risk of poor wound healing and even wound expansion. For dry, uninfected wounds, the literature advocates for nonsurgical debridement (eg, enzymatic and autolytic).[49]

Hyperbaric oxygen therapy may be considered for recalcitrant wounds. It entails delivery of 100% oxygen at 2 to 2.5 times the atmospheric pressure in a sealed chamber for approximately 2 hours and aims to correct the ischemia pervasive in calciphylaxis wounds. In a retrospective study of 34 patients, 20 patients (58%) showed improvement in their wounds, with more than half achieving complete healing.[50] However, 12 patients (35%) experienced deterioration and 2 patients (6%) had no change, and most of them died within a year.

Pain management is crucial but is often challenging as pain may not be responsive to even high-dose analgesics.[13] Morphine should be avoided in patients with calciphylaxis because it has active metabolites that accumulate in renal failure and cause respiratory depression.[51] Fentanyl and methadone are preferred opioids because they have no active metabolites that accumulate in renal failure. Again, sodium thiosulfate can provide significant pain relief even before improvement in skin lesions.

CONCLUSIONS

Calciphylaxis is a cutaneous ischemic infarct caused by total occlusion of blood vessels in the subcutaneous fat and dermis. The occlusion is initiated by vascular wall calcification and is completed by thrombosis, resulting in painful plaques and ulcers. Until recently, treatments have been limited to controlling its risk factors and optimizing wound care. However, recent advances in our understanding of the mechanism of vascular calcification in calciphylaxis have identified promising potential therapeutic targets.

As providers gain more insight into how calciphylaxis develops and identify additional novel therapeutic targets, it may soon be possible to effectively treat what has been a highly debilitating illness since its first description half a century ago.

PRACTICE PEARLS

- Calciphylaxis is a debilitating, life-threatening ischemic skin disease that primarily occurs in patients with ESRD. It is caused by ectopic bone formation in the subcutaneous and dermal blood vessel walls, leading to intraluminal thrombosis and occlusion.
- Diagnosis can be made on clinical grounds alone, when a dialysis patient presents with indurated, painful, tender plaques or ulcers that appear on the abdomen and/or legs. Skin biopsy may be necessary to differentiate calciphylaxis from one of its mimics and should be strongly considered in patients exhibiting the characteristic lesions in the absence of ESRD.
- The most common clinical scenario that gives rise to calciphylaxis is a lack of molecular calcification inhibitors in the vessel walls. This deficiency is most often attributable to a lack of vitamin K.
- Prevention consists of maintaining normal calcium and phosphate levels and avoiding warfarin, although data are sparse.
- Treatment consists of a three-pronged approach: (1) optimizing wound management with judicious use of surgical debridement and hyperbaric oxygen therapy, (2) halting progression of vessel wall calcification by ameliorating risk factors of calciphylaxis, and (3) reversing vessel wall calcification with sodium thiosulfate or vitamin K supplementation.

References

1. Fine A, Zacharias J. Calciphylaxis is usually non-ulcerating: risk factors, outcome and therapy. Kidney Int 2002;61(6):2210-7.
2. Selye H, Gentile G, Prioreschi P. Cutaneous molt induced by calciphylaxis in the rat. Science 1961;134(3493):1876-7.
3. Anderson DC, Stewart WK, Piercy DM. Calcifying panniculitis with fat and skin necrosis in a case of uraemia with autonomous hyperparathyroidism. Lancet 1968;2(7563):323-5.
4. Rees JK, Coles GA. Calciphylaxis in man. Br Med J 1969;2(5658):670-2.
5. Weenig RH. Pathogenesis of calciphylaxis: Hans Selye to nuclear factor kappa-B. J Am Acad Dermatol 2008;58(3):458-71.
6. Angelis M, Wong LL, Myers SA, Wong LM. Calciphylaxis in patients on hemodialysis: a prevalence study. Surgery 1997;122(6):1083.
7. Brandenburg VM, Kramann R, Rothe H, et al. Calcific uraemic arteriolopathy (calciphylaxis): data from a large nationwide registry. Nephrol Dial Transplant 2017;32:126-32.
8. Nigwekar SU, Zhao S, Wenger J, et al. A nationally representative study of calcific uremic arteriolopathy risk factors. J Am Soc Nephrol 2016;27:3421-9.
9. United States Renal Data System. 2017 ADR Chapters. 2017. www.usrds.org/2017/view. Last accessed February 22, 2019.
10. Bajaj R, Courbebaisse M, Kroshinsky D, Thadhani RI, Nigwekar SU. Calciphylaxis in patients with normal renal function: a case series and systematic review. Mayo Clin Proc 2018;93(9):1202-12.
11. Nigwekar SU, Bloch DB, Nazarian RM, et al. Vitamin K-dependent carboxylation of matrix Gla protein influences the risk of calciphylaxis. J Am Soc Nephrol 2017;28(6):1717-22.
12. Weenig RH, Sewell LD, Davis MD, McCarthy JT, Pittelkow MR. Calciphylaxis: natural history, risk factor analysis, and outcome. J Am Acad Dermatol 2007;56:569-79.
13. Polizzotto MN, Bryan T, Ashby MA, Martin P. Symptomatic management of calciphylaxis: a case series and review of the literature. J Pain Symptom Manage 2006;32:186-90.
14. Nigwekar SU, Thadhani R, Brandenburg VM. Calciphylaxis. N Engl J Med 2018;379(4):399-400.
15. Champion RH. Livedo reticularis. A review. Br J Dermatol 1965;77:167-79.
16. Sajjan VV, Lunge S, Swamy MB, Pandit AM. Livedo reticularis: a review of the literature. Indian Dermatol Online J 2015;6(5):315–21.

17. Schurgers LJ, Uitto J, Reutelingsperger CP. Vitamin K-dependent carboxylation of matrix Gla-protein: a crucial switch to control ectopic mineralization. Trends Mol Med 2013;19:217-26.
18. Bessueille L, Fakhry M, Hamade E, Badran B, Magne D. Glucose stimulates chondrocyte differentiation of vascular smooth muscle cells and calcification: a possible role for IL-1β. FEBS Lett 2015;589(19 Pt B):2797-804.
19. Chen NX, O'Neill K, Akl NK, Moe SM. Adipocyte induced arterial calcification is prevented with sodium thiosulfate. Biochem Biophys Res Commun 2014;449:151-6.
20. Kramann R1, Brandenburg VM, Schurgers LJ, et al. Novel insights into osteogenesis and matrix remodelling associated with calcific uraemic arteriolopathy. Nephrol Dial Transplant 2013;28(4):856-68.
21. Luo G, Ducy P, McKee MD, et al. Spontaneous calcification of arteries and cartilage in mice lacking matrix GLA protein. Nature 1997;386:78-81.
22. Cranenburg EC, Schurgers LJ, Uiterwijk HH, et al. Vitamin K intake and status are low in hemodialysis patients. Kidney Int 2012;82(5):605-10.
23. El-Azhary RA, Patzelt MT, McBane RD, et al. Calciphylaxis: a disease of pannicular thrombosis. Mayo Clin Proc 2016;91:1395-402.
24. Dobry AS, Ko LN, St John J, Sloan JM, Nigwekar S, Kroshinsky D. Association between hypercoagulable conditions and calciphylaxis in patients with renal disease: a case-control study. JAMA Dermatol 2018;154:182-7.
25. Ghosh T, Winchester DS, Davis MDP, El-Azhary R, Comfere NI. Early clinical presentations and progression of calciphylaxis. J Dermatol 2017;56(8):856-86.
26. Hafner J. Calciphylaxis and Martorell hypertensive ischemic leg ulcer: same pattern—one pathophysiology. Dermatology 2016;232(5):523-33.
27. Brandenburg VM, Evenepoel P, Floege J, et al. Lack of evidence does not justify neglect: how can we address unmet medical needs in calciphylaxis? Nephrol Dial Transplant 2016;31(8):1211-9.
28. Ha CT, Nousari HC. Surgical pearl: double-trephine punch biopsy technique for sampling subcutaneous tissue. J Am Acad Dermatol 2003;48:609-10.
29. Nigwekar SU, Kroshinsky D, Nazarian RM, et al. Calciphylaxis: risk factors, diagnosis, and treatment. Am J Kidney Dis 2015;66(1):133-46.
30. Paul S, Rabito CA, Vedak P, Nigwekar SU, Kroshinsky D. The role of bone scintigraphy in the diagnosis of calciphylaxis. JAMA Dermatol 2017;153(1):101-3.
31. Shmidt E, Murthy NS, Knudsen JM, et al. Net-like pattern of calcification on plain soft-tissue radiographs in patients with calciphylaxis. J Am Acad Dermatol 2012;67(6):1296-301.
32. Nigwekar SU. Calciphylaxis. Curr Opin Nephrol Hypertens 2017;26(4):276-81.
33. Sprague SM. Painful skin ulcers in a hemodialysis patient. Clin J Am Soc Nephrol 2014;9:166-73.
34. Keskar V, Sood MM. Use of oral anticoagulation in the management of atrial fibrillation in patients with ESRD: con. Clin J Am Soc Nephrol 2016;11:2085–92.
35. King BJ, El-Azhary RA, McEvoy MT, et al. Direct oral anticoagulant medications in calciphylaxis. Int J Dermatol 2017;56(10):1065-70.
36. Klil-Drori AJ, Tagalakis V. Direct oral anticoagulants in end-stage renal disease. Semin Thromb Hemost 2018;44(4):353-63.
37. Cicone JS, Petronis JB, Embert CD, Spector DA. Successful treatment of calciphylaxis with intravenous sodium thiosulfate. Am J Kidney Dis 2004;43(6):1104-8.
38. Hayden MR, Goldsmith DJ. Sodium thiosulfate: new hope for the treatment of calciphylaxis. Semin Dial 2010;23(3):258-62.
39. Sowers KM, Hayden MR. Calcific uremic arteriolopathy: pathophysiology, reactive oxygen species and therapeutic approaches. Oxid Med Cell Longev 2010;3(2):109-21.
40. Pasch A, Schaffner T, Huynh-Do U, Frey BM, Frey FJ, Farese S. Sodium thiosulfate prevents vascular calcifications in uremic rats. Kidney Int 2008;74(11):1444-53.
41. Strazzula L, Nigwekar SU, Steele D, et al. Intralesional sodium thiosulfate for the treatment of calciphylaxis. JAMA Dermatol 2013;149:946-9.
42. Nigwekar SU, Brunelli SM, Meade D, Wang W, Hymes J, Lacson EJr. Sodium thiosulfate therapy for calcific uremic arteriolopathy. Clin J Am Soc Nephrol 2013;8:1162-70.
43. Mazhar AR, Johnson RJ, Gillen D, et al. Risk factors and mortality associated with calciphylaxis in end-stage renal disease. Kidney Int 2001:60(1):324-32.
44. Schurgers LJ, Spronk HM, Soute BA, Schiffers PM, DeMey JG, Vermeer C. Regression of warfarin-induced medial elastocalcinosis by high intake of vitamin K in rats. Blood 2007;109(7):2823-31.
45. Shea MK, O'Donnell CJ, Hoffmann U, et al. Vitamin K supplementation and progression of coronary artery calcium in older men and women. Am J Clin Nutr 2009;89:1799-807.
46. Brandenburg VM, Reinartz S, Kaesler N, et al. Slower progress of aortic valve calcification with vitamin k supplementation: results from a prospective interventional proof-of-concept study. Circulation 2017;135(21):2081-3.
47. Christiadi D, Singer RF. Calciphylaxis in a dialysis patient successfully treated with high-dose vitamin K supplementation. Clin Kidney J 2018;11(4):528-9.
48. McCarthy JT, El-Azhary RA, Patzelt MT, et al. Survival, risk factors, and effect of treatment in 101 patients with calciphylaxis. Mayo Clin Proc 2016;91:1384-94.
49. Martin R. Mysterious calciphylaxis: wounds with eschar—to debride or not to debride? Ostomy Wound Manage 2004;50:64–6.
50. An J, Devaney B, Ooi KY, Ford S, Frawley G, Menahem S. Hyperbaric oxygen in the treatment of calciphylaxis: a case series and literature review. Nephrology 2015;20:444-50.
51. Dean M. Opioids in renal failure and dialysis patients. J Pain Symptom Manage 2004;28(5):497-504.

For more than 138 additional continuing education articles related to Skin and Wound Care topics, go to NursingCenter.com/CE.

CE CONNECTION

CONTINUING MEDICAL EDUCATION INFORMATION FOR PHYSICIANS

Lippincott Continuing Medical Education Institute, Inc., is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Lippincott Continuing Medical Education Institute, Inc., designates this journal-based CME activity for a maximum of 1 *AMA PRA Category 1 Credit™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

PROVIDER ACCREDITATION INFORMATION FOR NURSES

Lippincott Professional Development will award 1.5 contact hours including 0.5 pharmacology credits for this continuing nursing education activity.

LPD is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

This activity is also provider approved by the California Board of Registered Nursing, Provider Number CEP 11749 for 1.5 contact hours. LWW is also an approved provider by the District of Columbia, Georgia, and Florida CE Broker #50-1223.

OTHER HEALTH PROFESSIONALS

This activity provides ANCC credit for nurses and *AMA PRA Category 1 Credit™* for MDs and DOs only. All other healthcare professionals participating in this activity will receive a certificate of participation that may be useful to your individual profession's CE requirements.

CONTINUING EDUCATION INSTRUCTIONS

- Read the article beginning on page 205. For nurses who wish to take the test for CNE contact hours, visit http://nursing.ceconnection.com. For physicians who wish to take the test for CME credit, visit http://cme.lww.com. Under the Journal option, select *Advances in Skin and Wound Care and click on the title of the CE activity.*
- You will need to register your personal CE Planner account before taking online tests. Your planner will keep track of all your Lippincott Professional Development online CE activities for you.
- There is only one correct answer for each question. A passing score for this test is 13 correct answers. If you pass, you can print your certificate of earned contact hours or credit and access the answer key. Nurses who fail have the option of taking the test again at no additional cost. Only the first entry sent by physicians will be accepted for credit.

Registration Deadline: April 30, 2021 (physicians); March 5, 2021 (nurses).

PAYMENT

- The registration fee for this CE activity is $17.95 for nurses; $22.00 for physicians.