Am J Clin Dermatol (2018) 19:599–608
https://doi.org/10.1007/s40257-018-0361-x

REVIEW ARTICLE

An Update on Calciphylaxis

José Alberto García-Lozano[1] · Jorge Ocampo-Candiani[1] · Sylvia Aide Martínez-Cabriales[1] · Verónica Garza-Rodríguez[1]

Published online: 28 May 2018

Abstract Calciphylaxis, also known as calcific uremic arteriolopathy and uremic small artery disease with medial wall calcification and intimal hyperplasia, is a multifactorial cutaneous vascular disease characterized by chronic, painful, non-healing wounds that occur frequently in patients with chronic kidney disease, predominantly in those with end-stage renal disease. The pathogenesis remains unclear, and the development of calciphylaxis lesions depends on medial calcification, intimal fibrosis of arterioles and thrombotic occlusion. Despite an increase in reports of calciphylaxis in the literature and clinical recognition of demographic characteristics and risk factors associated with calciphylaxis, it remains a poorly understood disease with high morbidity and mortality. In this review, we analyze and summarize the clinical manifestations, pathogenesis and pathophysiology, histopathology, differential diagnosis, diagnostic workup and treatment modalities for calciphylaxis. Because of the lack of consensus regarding the optimal approach to and treatment of this disorder, a high degree of clinical suspicion, early diagnosis, and multimodal and multidisciplinary treatment in collaboration with dermatology, nephrology, wound care, nutrition and pain management specialties may improve survival in patients with calciphylaxis.

Key Points

Calciphylaxis is a multifactorial cutaneous vascular disease characterized by chronic, painful, non-healing wounds that occur frequently in patients with chronic kidney disease.

Histological confirmation is recommended and remains the gold standard for definitive diagnosis; however, in cases where there is a high clinical suspicion of calciphylaxis, prompt aggressive treatment should be initiated and histological confirmation can be reserved.

Calciphylaxis is a complex disease that requires collaboration among multiple specialties, including dermatology, nephrology, wound care, nutrition and pain management, for adequate treatment.

Sodium thiosulfate is a chelating vasodilator and an antioxidant that has been shown to contribute significantly to healing of calciphylaxis lesions and has become one of the primary treatment modalities.

1 History

Calciphylaxis is a poorly understood and highly morbid cutaneous vascular disease. Bryant and White first described its association with uremia in 1898 [1], but it was not until 1962 that Hans Selye and colleagues originated the term calciphylaxis after inducing tissue calcification in rats

✉ Verónica Garza-Rodríguez
verogarzardz@hotmail.com

[1] Department of Dermatology, University Hospital "Dr. José Eleuterio González", Autonomous University of Nuevo León, Av. Madero y Gonzalitos S/N 64460 Col. Mitras Centro, Monterrey, Mexico

that underwent sensitizing factors followed by a subsequent trigger or "challenger." They believed this response of tissue calcification was an adaptive or "phylactic" reaction; hence, the term calciphylaxis (calcification and phylaxis) was coined [2]. In 1963, Eisenberg and Bartholow reported a case of extensive metastatic calcification in a patient with chronic renal failure, representing the human counterpart of calciphylaxis [3].Within a few years, Rees and Cole published another case of calciphylaxis in a patient with renal failure [4]. Over the next several years, other cases of calciphylaxis were also reported [5–8].

2 Introduction and Definition

Calciphylaxis, also known as calcific uremic arteriolopathy and uremic small artery disease with medial wall calcification and intimal hyperplasia, is a multifactorial cutaneous vascular disease that occurs frequently in patients with chronic kidney disease (CKD), predominantly in those with end-stage renal disease (ESRD). Nonetheless, it has also been documented in patients with normal renal function with normal calcium and phosphate metabolism [9, 10].

The reported prevalence of calciphylaxis is 1–4% among patients with ESRD on dialysis or hemodialysis; however, recent studies demonstrate that the incidence is $< 1\%$, in contrast to the rates reported in previous publications [11–14]. Nevertheless, the prevalence and incidence of this vascular disease still remains unknown. Risk factors for the development of calciphylaxis are numerous and predominantly include female gender, diabetes mellitus, hyperphosphatemia, CKD/ESRD, warfarin exposure, and liver disease, among others (Table 1) [15–18]. Despite an increase in reports of calciphylaxis in the literature and clinical recognition of demographic characteristics and risk factors associated with calciphylaxis, it remains a poorly understood disease with high morbidity and mortality [9, 19].

Table 1 Demographic characteristics and risk factors associated with calciphylaxis

Female gender
Diabetes mellitus
CKD/ESRD
Warfarin exposure
Liver disease
Obesity
Hypercalcemia
Hyperphosphatemia

Less common risk factors: Caucasian race, calcium-phosphate binders, calcium-phosphate product > 70 mg^2/dL^2, vitamin D supplementation, protein C and/or S deficiency, corticosteroids, erythropoietin and iron dextran

CKD chronic kidney disease, *ESRD* end-stage renal disease

3 Clinical Manifestations

Calciphylaxis generally presents with chronic, painful, non-healing wounds [20]. According to the retrospective review of Weenig et al. [22], patients had predominantly five different types of cutaneous lesions as follows: necrotic ulcers, livedo racemosa, hemorrhagic patches, hemorrhagic bullae and indurated plaques. However, the range of clinical presentations and lesional morphologies seen in early stages of calciphylaxis is broad, and subcutaneous nodules, painful cellulitis-like erythematous plaques, among others, should be considered [21]. The skin of proximal regions (e.g., the thigh) was more commonly affected than distal areas [22]. Jeong et al. [20] described calciphylaxis lesions as tender, indurated subcutaneous plaques with overlying livedo racemosa that progress to non-healing stellate-shaped ulcers covered by black eschar (Fig. 1). The lesions normally involve adipose-rich areas (trunk, breasts, abdominal pannus, flanks, buttocks and proximal lower extremities) [20]; however, genital and digital involvement have also been reported [23–25]. Cutaneous ulcerations are commonly observed, and a morbidity and mortality of up to 50–80% has been reported with cutaneous ulcerations, due to septic complications [26–28].

In our experience, when there is a patient with ESRD on dialysis who complains of a painful necrotic ulcer, calciphylaxis should always be considered as a differential diagnosis, and prompt intervention should be performed.

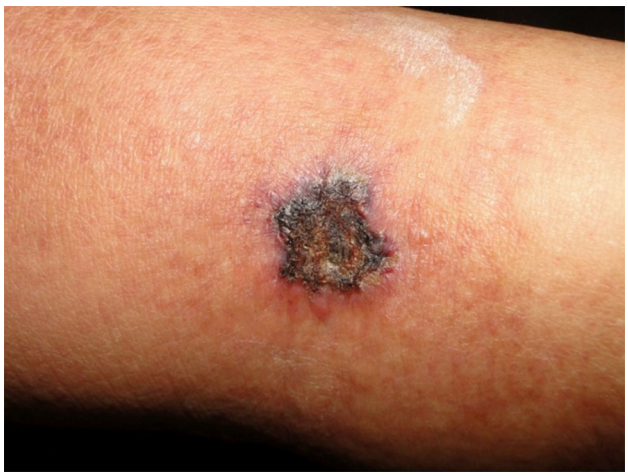

Fig. 1 Calciphylaxis: a stellate-shaped necrotic plaque

4 Pathogenesis and Pathophysiology

It is believed that calciphylaxis develops secondary to an imbalance between factors that favor calcification and those that prevent it [11]. According to the existing model for vascular calcification, the interaction of uremia [hyperphosphatemia, reactive oxygen species (ROS) and uremic toxins] and the decrease in local vascular calcification inhibitory proteins [matrix Gla protein (MGP) and alpha 2-Heremans-Schmid glycoprotein (fetuin-A)] initiate the differentiation of vascular smooth muscle cells (VSMCs) into an osteoblast-like phenotype or chondrocytes [9, 20, 29].

An imbalance in the mineral content of the renal system, such as hyperphosphatemia, elevated calcium-phosphorus products, hyperparathyroidism, and vitamin D deficiency, is the most common risk factor associated with calciphylaxis [11, 20]. Patients with CKD/ESRD develop chronic hyperparathyroidism leading to high-turnover bone disease, hypophosphatemia, hypercalcemia, and extraosseous (vascular) calcium deposition. On the other hand, chronic hypoparathyroidism, which causes low-turnover bone disease and osseous tissue, leads to decreased capacity to absorb calcium and decreased phosphate levels; paradoxically, this increases mineral content in the blood and contributes to the development of vascular calcification [30–33].

Bone morphogenic proteins belong to the transforming growth factor superfamily. These proteins are involved in inducing de novo bone formation, osteoclast differentiation and extraosseous calcification [34–37]. Bone morphogenic protein-4 (BMP-4) is another factor involved in the pathogenesis of calciphylaxis, as it promotes calcification [38]. The action of BMP-4 is believed to be dependent on ROS that activate nuclear factor kappa B (NF-κB) [38, 39]. NF-κB is an extremely important transcription factor for different cellular functions, including normal bone development, osteoclast differentiation and bone mineral resorption. Autoimmune inflammatory states, atherosclerosis and bone mineral loss are associated with high NF-κB activity. This increased NF-κB activity causes osseous mineral loss and extraosseous mineral deposition (vascular calcification) [30].

Chronic inflammatory states, including CKD/ESRD, are associated with bone mineral loss and vascular calcification [30]. This is secondary to increased activity of NF-κB, receptor activator of NF-κB (RANK) and its ligand (RANKL), suggesting the role of the NF-κB osteoprotegerin/RANK/RANKL axis in bone homeostasis and vascular calcification [9, 11, 40]. More importantly, patients with ESRD on hemodialysis also have low levels of fetuin-A, a human circulating inhibitor of calcification, contributing to the imbalance of factors that promote and inhibit calcification [11, 41]. Decreased levels of circulating inhibitors of calcification in ESRD together with factors such as uremia and hyperphosphatemia are thought to trigger the differentiation of VSMCs into osteoblasts, producing vascular calcification.

Nonetheless, vascular calcification alone does not lead to calciphylaxis. The development of calciphylaxis lesions depends on medial calcification, intimal fibrosis of arterioles and thrombotic occlusion [20]. These processes occur after a period of sensitization induced by factors that favor calcification [parathyroid hormone (PTH), vitamin D, and high calcium/phosphorus] and a period of challenge such as trauma, surgery or any other event associated with an increase in inflammatory cytokines that trigger the three prothrombotic factors of Virchow (hypercoagulability, stasis and endothelial injury) [11, 30, 42].

5 Histopathology

Despite the fact that calciphylaxis is a clinical diagnosis, histological confirmation is recommended and remains the gold standard for definitive diagnosis [9]. The pathognomonic histological characteristics of epidermal ulceration, focal dermal necrosis, and vascular calcification are observed in biopsies of calciphylaxis lesions [9, 43]. Calcium salts are easily recognized in hematoxylin and eosin sections by their intense uniform basophilia; if necessary, they can be confirmed by von Kossa's silver stain, which blackens the deposits, demonstrating an incipient stippled pattern of microvascular calcification [44], or by the Alizarin red stain, which also allows detection of calcium in an orange-red color that may be birefringent [45]. The dominant pathology is localized to the subcutaneous fat [11], where the calcification involves capillaries, venules, arterioles, and small arteries of subcutaneous fat. Other common findings include intimal hyperplasia, inflammatory responses, endovascular fibrosis, thrombosis, fat necrosis, acute and chronic calcifying panniculitis and extravascular calcium deposition [9, 19, 22, 46, 47] (Fig. 2).

6 Differential Diagnosis

For early and accurate diagnosis of calciphylaxis, a high degree of suspicion is required [11, 48]. Other pathologies must be considered and ruled out during the diagnosis of calciphylaxis, including cholesterol embolism syndrome, warfarin- and heparin-induced skin necrosis, anti-phospholipid syndrome, nephrogenic systemic fibrosis,

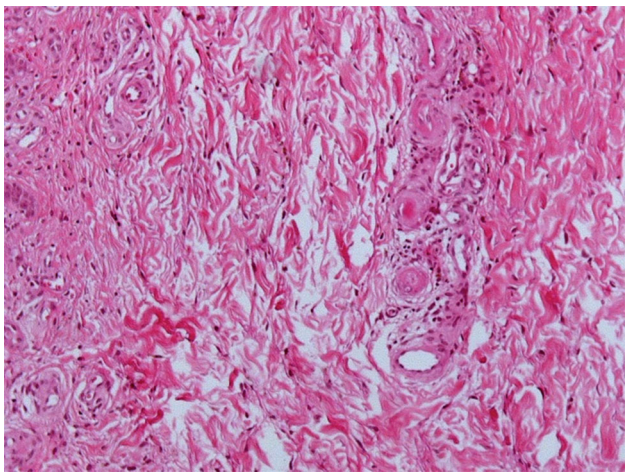

Fig. 2 Histopathology: there are several thrombosed vessels, intimal fibroblastic proliferation and degenerated connective tissue (hematoxylin and eosin)

pyoderma gangrenosum, cryoglobulinemia and vasculitis [11, 20, 48].

7 Diagnostic Workup

The diagnosis of calciphylaxis is predominantly clinical; therefore, a detailed medical history focused on risk factors and a thorough physical examination should always be performed to identify additional skin lesions [49]. In a patient with CKD/ESRD (or any other risk factor), the triad of intense pain associated with cutaneous lesions and palpation of firm calcified subcutaneous tissue is consistent with the diagnosis of calciphylaxis until proven otherwise [49, 50]. Histological confirmation of a skin biopsy specimen remains the gold standard for definitive diagnosis, especially in atypical clinical scenarios [49]. However, deep incisional cutaneous biopsy may induce ulceration in the area of the incision, increasing the risk of infection, poor healing and consequently escalating the risk of sepsis and death [51]. Therefore, in cases where there is a high clinical suspicion of calciphylaxis, promptly aggressive treatment should be initiated and histological confirmation can be reserved. In our experience, a punch biopsy (3–5 mm) of the edge of the lesion, providing an adequate sample of dermis and subcutaneous fat, is safer and is the preferred approach for histological confirmation of calciphylaxis.

Laboratory tests should be performed whenever there is clinical suspicion of calciphylaxis. These tests will help the physician further evaluate potential risk factors and exclude other disorders that may mimic the presentation of calciphylaxis. These tests should evaluate renal function, mineral bone parameters, presence of infection, coagulation factors, hypercoagulability, inflammation, autoimmune disease and malignancy [49].

Non-invasive imaging tools (plain X-rays and three-phase nuclear bone scans), procedures (bone scintigraphy) and biomarkers (circulating fetuin-A levels) have also been reported as useful tests in the diagnosis of calciphylaxis because of their ability to detect soft tissue microcalcifications [41, 52–54]. Recently, there have been reports regarding the high sensitivity and specificity of three-phase technetium Tc99m methylene diphosphate bone scintigraphy for early diagnosis of calciphylaxis [55, 56]. However, none of these non-invasive tools have been systematically evaluated and therefore cannot be recommended for routine workup of patients with suspected calciphylaxis.

8 Treatment

Calciphylaxis is a very complex disease that requires collaboration among multiple specialties for adequate treatment, including dermatology, nephrology, wound care, nutrition and pain management. The main objectives are to heal vascular calcifications and prevent septic complications leading to death. There have been many proposed treatments for the management of calciphylaxis; however, there are currently no clinical practice guidelines for the management of this disease, and the majority of reports supporting these interventions come from retrospective case reports, case series and cohort studies [49]. In our experience, a multimodal and multidisciplinary approach that incorporates multiple specialties leads to the best results. Figure 3 shows a flowchart of the approach proposed by the authors for the diagnosis and treatment of calciphylaxis.

8.1 Pain Management

Since the primary complaint in patients with calciphylaxis is intense pain, appropriate palliative measures and consultation with a pain management specialist (especially in patients with CKD/ESRD) need to be considered. Benzodiazepines and narcotic analgesics such as sufficient doses of opioids and ketamine have been recommended [57]. Occasionally, fentanyl patches may be preferred as a first-line method of pain control [36]. In cases of opioid-resistant pain, levomethadone has been reported to be successful [58].

8.2 Wound Care

Wound care should be a cornerstone of therapy in all patients and should include removal of necrotic tissue, aiding wound healing and preventing infection (Table 2) [20, 49]. Removing necrotic tissue is recommended to allow proper healing, and it is preferably performed when

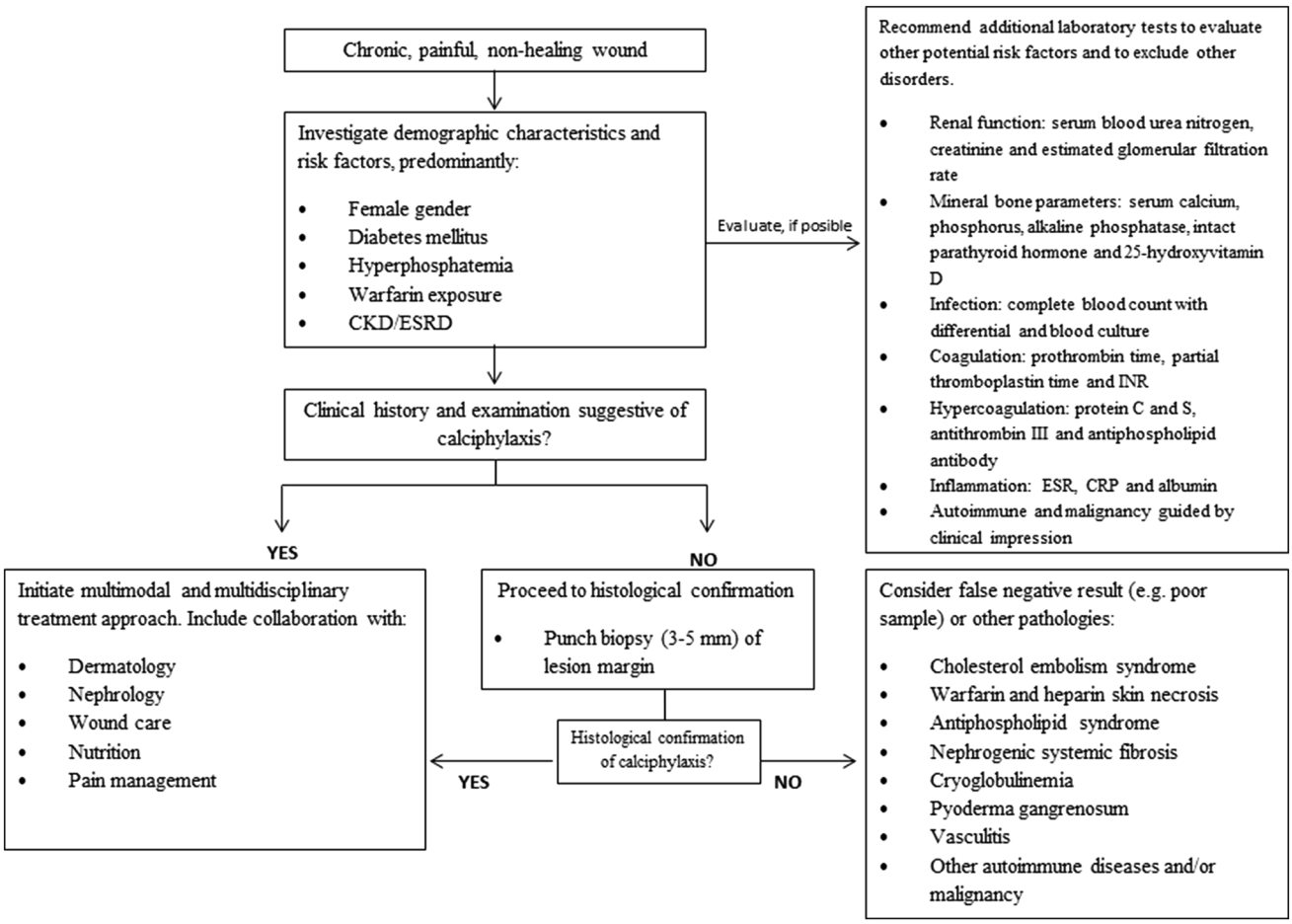

Fig. 3 Calciphylaxis diagnostic and therapeutic approach. *CKD* chronic kidney disease, *ESRD* end-stage renal disease, *INR* international normalized ratio, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein

no signs of active ischemia are found [11, 20]. Surgical wound debridement has been a matter of debate; those who oppose debridement fear aggravation of cutaneous lesions and believe that drug therapy is capable of preventing fatal outcomes [59, 60]. However, considering that the primary cause of mortality in calciphylaxis is sepsis, surgical debridement of infected lesions may be a reasonable approach, except in penile disease, due to a worse outcome [61]. A retrospective study of 64 patients (49 dialysis cases vs. 15 non-dialysis cases) with calciphylaxis was conducted by Weenig et al. to better understand the natural history, risk factors and variables that may influence survival in patients with calciphylaxis [22]. An estimated 1-year survival rate of 61.6% was observed in 17 patients who received surgical debridement, compared with 27.4% in 46 patients who did not undergo surgical debridement; however, the difference was not statistically significant [22]. These patients were not stratified by disease severity and overall illness, and the results need to be interpreted with caution since patients with more severe disease were unlikely to undergo general anesthesia and surgical intervention. Other treatment options include maggot debridement, chemical debridement (collagenase, medical honey products), negative pressure wound therapy, hyperbaric oxygen and skin grafting [62–68].

8.3 Sodium Thiosulfate

Sodium thiosulfate (STS) has become one of the primary treatment modalities for healing calciphylaxis lesions [69–71]. The mechanism of action of calciphylaxis treatment is not yet fully understood. STS chelates calcium from precipitates in the skin, subcutaneous tissues and organs. The resulting calcium thiosulfate compound is more soluble than other calcium salts and is believed to be removed by dialysis. The other proposed mechanism involves its antioxidant activity, where STS donates electrons that repair damaging ROS. The latter restores endothelial production of nitric oxide, promoting reperfusion by vasodilation [35, 72]. While there is no standardized dose of STS, reported effective dosages range from 5 to 25 g thrice a week, during or after hemodialysis,

Table 2 Treatment options for calciphylaxis

Sodium thiosulfate (first-line therapy) [69–79, 82–84]
Patients on dialysis or hemodialysis: 5–25 g IV 3 times per week[a]
Patients with normal renal function: 5–25 g IV 3 times per week or daily[b]
Intralesional: 1–3 cc of 250 mg/mL weekly[c]
Wound care [9, 11, 20, 49, 62–68]
Hyperbaric oxygen (second-line therapy): 2.5 atm or high-flow oxygen therapy (10–15 L/min) 90 min per day for 25 sessions[d]
Debridement:
Surgical debridement
Maggot debridement
Chemical debridement
Other:
Prevention of infection
Antibiotics in the presence of infection
Negative pressure wound therapy
Skin grafting
Correction of calcium and phosphorus abnormalities [14, 20, 26, 49, 85]
Cinacalcet[e]:
30 mg daily for 5 months
60–120 mg daily for 9 months
Bisphosphonates:
Pamidronate 90 mg IV followed by 30 mg IV weekly (6 times)
Etidronate 200 mg PO daily for 2 weeks
Alendronate 70 mg weekly
Risedronate 35 mg weekly
Parathyroidectomy
Anticoagulation [88–91]
Unfractionated heparin[f]:
Subcutaneous 5000 IU twice daily
Continuous IV infusion
Tinzaparin[f]: Subcutaneous 175 IU/kg once daily
Hypercoagulable states: Infusion of 10 mg of tissue plasminogen activator IV during a 4-h period daily for 14 days[g]
Renal replacement therapy [20, 49, 92, 93]
Dialysis/hemodialysis: Increase duration and frequency per week[h]
Kidney transplantation

atm atmosphere, *cc* cubic centimeter, *IV* intravenous, *PO* per os/by mouth

[a]Therapy should be administered during the last dose of dialysis and must be continued until complete resolution of symptoms is achieved. Authors recommend that administration of sodium thiosulfate should continue for at least 2 months beyond complete healing of cutaneous lesions

[b]Response to daily treatment with sodium thiosulfate in patients with normal renal function has also been reported. Individualize each case

[c]Reports show that intralesional sodium thiosulfate has no known limitations in volume and is lesion dependent. Consider individualizing each case

[d]Some authors recommend 20–40 sessions

[e]Use in patients in hemodialysis with moderate to severe secondary hyperparathyroidism

[f]Adjust to maintain the activated partial thromboplastin time at 1.5–2 times the normal control value

[g]Data limited to a few reports. Individualize each case

[h]Individualize each case

maintained for up to 2 months beyond complete healing of cutaneous lesions [69–71, 73–75]. Improvements in cutaneous ulcers and pain have been observed in 70% of patients on hemodialysis [26, 76]. Daily intravenous (IV) STS has also been used successfully in patients with normal renal function [77–79]. There are no specific

contraindications to IV STS [72]. Common side effects of this agent are transient hypocalcemia, hypernatremia, QT prolongation, anion gap metabolic acidosis, headaches, nausea, and vomiting, among others [72, 80, 81]. Careful monitoring for transient adverse effects is therefore of utmost importance. The use of intralesional STS in the active borders of the ulcer to prevent these adverse events has been previously reported, with pain during injections being the main side effect [82–84]. However, larger studies are needed to determine the proper dose and frequency and the population who would benefit from this therapy.

8.4 Correction of Calcium and Phosphorus Abnormalities

Patients with ESRD have calcium, phosphorus, PTH and vitamin D abnormalities leading to calciphylaxis lesions. One of the primary goals in the treatment of calciphylaxis is controlling these abnormal processes through regulation of these substrates. One common strategy to maintain control of these substances is through intense hemodialysis sessions (increasing the duration and frequency) [49]. When vascular calcification is induced by PTH, cinacalcet at dosages from 30 to 180 mg/day has shown the best results for normalizing secondary hyperparathyroidism [14]. Parathyroidectomy is a surgical option for controlling PTH levels and has been demonstrated to be effective in some isolated cases [85]. Potential risks of parathyroidectomy include severe hypocalcemia, potential poor wound healing, surgical wound infection, hungry bone syndrome and development of adynamic bone disease [49, 86]. For these reasons, medical management is preferred over surgical parathyroidectomy by some authors, considering that the latter leads to worse outcomes [86, 87]. Other strategies include the use of bisphosphonates, including oral etidronate disodium and IV pamidronate, ibandronate 150 mg monthly, alendronate 70 mg weekly or risedronate 35 mg weekly, non-calcium/non-aluminum phosphate binders (sevelamer hydrochloride and lanthanum carbonate) and paricalcitol [20, 26].

8.5 Anticoagulation

In some patients with calciphylaxis, there is an interaction between hypercoagulability, vascular calcification and development of lesions. Although some may benefit from anticoagulation (those with known hypercoagulable states), full anticoagulation in all patients with calciphylaxis is not currently recommended because of the lack of efficacy, safety and non-warfarin options in patients with ESRD [20]. In patients with comorbidities necessitating chronic anticoagulation and who subsequently develop calciphylaxis, providing therapeutic coagulation may be a great challenge. Currently, there are no specific protocols for this unique subset of patients with renal, cardiac and dermatological disease, and the guidelines for the general population are largely inappropriate for these patients [26]. Since warfarin has been demonstrated to worsen calciphylaxis lesions, full-intensity subcutaneous unfractionated heparin (UFH) and tinzaparin have become alternative anticoagulant agents for patients with kidney disease, cardiac comorbidities and calciphylaxis [88, 89]. Hospitalization and continuous UFH infusion may be the safest method to provide full anticoagulation while calciphylaxis lesions are healing; however, risk of nosocomial infection should always be considered. Lastly, it is of utmost importance to execute proper workup for an underlying hypercoagulable state in all patients with calciphylaxis, as these diseases place patients at a greater risk of thrombotic events and may aggravate calciphylaxis lesions [20]. Daily low-dose infusion of tissue plasminogen activator may be a useful adjunctive treatment in the management of patients with calciphylaxis with an underlying hypercoagulable state because it lyses clots and restores perfusion [90, 91].

8.6 Kidney Transplantation

Since calciphylaxis develops largely from mineral imbalances secondary to malfunctioning kidneys, it has been hypothesized that the correction of these imbalances through kidney transplantation should restore these minerals to normal levels and theoretically prevent the progression or development of calciphylaxis [20]. Some reports have demonstrated the resolution of calciphylaxis lesions, while others report new onset of calciphylaxis lesions after transplantation [92, 93]. However, the details of this treatment modality remain unclear, and further studies are needed to resolve these uncertainties.

9 Prognosis

The prognosis for patients with calciphylaxis is poor, with the 1-year survival rate failing to reach 50% and the 2-year survival rate approaching 20% [22]. Thus, early discussion with patients and their families regarding the prognosis and approach to future therapy is justified. Most of the deaths are due to sepsis secondary to infected ulcerations. If calciphylaxis involves the lower limbs, the mortality is approximately 20%. However, if calciphylaxis develops on the trunk, upper limbs or penis, the mortality may be as high as 60% [94]. It is very important to keep in mind that once an ulceration has developed, the mortality rate increases to greater than 80%, and patients typically die within the next 6–12 months [9, 22, 49, 95, 96]. Additionally, female sex and obesity have been associated with worse prognosis [97].

10 Conclusion

Calciphylaxis is a unique, debilitating and potentially life-threatening ischemic vasculopathy with a controversial and multifactorial pathogenesis primarily seen in patients with ESRD on hemodialysis. There is currently no consensus for the optimal approach to and treatment of this disorder. A high degree of clinical suspicion, early diagnosis, and multimodal and multidisciplinary treatment with collaboration between dermatology, nephrology, wound care, nutrition and pain management specialties may improve survival in patients with calciphylaxis.

Compliance with Ethical Standards

Funding No funding was received for the preparation of this article.

Conflict of interest José Alberto García-Lozano, Jorge Ocampo-Candiani, Silvia Aide Martínez-Cabriales and Verónica Garza-Rodríguez have no conflicts of interest.

References

1. Bryant JH. Case of calcification of the arteries and obliterative endarteritis associated with hydronephrosis in a child aged six months. Guys Hosp Rep. 1901;55:17.
2. Selye H. The dermatologic implications of stress and calciphylaxis. J Investig Dermatol. 1962;39(4):259–75.
3. Eisenberg E, Bartholow PV Jr. Reversible calcinosis cutis: calciphylaxis in man. N Engl J Med. 1963;268(22):1216–20.
4. Rees JK, Coles GA. Calciphylaxis in man. BMJ. 1969;2(5658):670–2.
5. Edelstein CL, Wickham MK, Kirby PA. Systemic calciphylaxis presenting as a painful, proximal myopathy. Postgrad Med J. 1992;68(797):209–11.
6. Bargman JM, Prichard SS. A usual peritoneal dialysis patient with an unusual skin disease. Perit Dial Int. 1995;15(6):252–8.
7. Budisavljevic MN, Cheek D, Ploth DW. Calciphylaxis in chronic renal failure. J Am Soc Nephrol. 1996;7(7):978–82.
8. Richens G, Piepkorn MW, Krueger GG. Calcifying panniculitis associated with renal failure. A case of Selye's calciphylaxis in man. J Am Acad Dermatol. 1982;6(4 Pt 1):537–9.
9. Sowers KM, Hayden MR. Calcific uremic arteriolopathy: pathophysiology, reactive oxygen species and therapeutic approaches. Oxid Med Cell Longev. 2010;3(2):109–21. https://doi.org/10.4161/oxim.3.2.11354.
10. Coates T, Kirkland GS, Dymock RB, Murphy BF, Brealey JK, Mathew TH, et al. Cutaneous necrosis from calcific uremic arteriolopathy. Am J Kidney Dis. 1998;32(3):384–91.
11. Yerram P, Chaudhary K. Calcific uremic arteriolopathy in end stage renal disease: pathophysiology and management. Ochsner J. 2014;14(3):380–5.
12. Angelis M, Wong LL, Myers SA, Wong LM. Calciphylaxis in patients on hemodialysis: a prevalence study. Surgery. 1997;122(6):1083–9 (**discussion 9–90**).
13. Fine A, Fontaine B. Calciphylaxis: the beginning of the end? Perit Dial Int. 2008;28(3):268–70.
14. Floege J, Kubo Y, Floege A, Chertow GM, Parfrey PS. The effect of cinacalcet on calcific uremic arteriolopathy events in patients receiving hemodialysis: the EVOLVE trial. Clin J Am Soc Nephrol. 2015;10(5):800–7. https://doi.org/10.2215/CJN.10221014.
15. Mazhar AR, Johnson RJ, Gillen D, Stivelman JC, Ryan MJ, Davis CL, et al. Risk factors and mortality associated with calciphylaxis in end-stage renal disease. Kidney Int. 2001;60(1):324–32. https://doi.org/10.1046/j.1523-1755.2001.00803.x.
16. Tian F, Patterson AT, Davick JJ, Ing SW, Kaffenberger BH, Gru AA. The cutaneous expression of vitamin K-dependent and other osteogenic proteins in calciphylaxis stratified by clinical features and warfarin use: a case control study. J Am Acad Dermatol. 2016;75(4):840–2 e1. https://doi.org/10.1016/j.jaad.2016.05.026.
17. 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(2):182–7. https://doi.org/10.1001/jamadermatol.2017.4920.
18. Nigwekar SU, Zhao S, Wenger J, Hymes JL, Maddux FW, Thadhani RI, et al. A nationally representative study of calcific uremic arteriolopathy risk factors. J Am Soc Nephrol. 2016;27(11):3421–9. https://doi.org/10.1681/ASN.2015091065.
19. Hayden MR, Goldsmith D, Sowers JR, Khanna R. Calciphylaxis: calcific uremic arteriolopathy and the emerging role of sodium thiosulfate. Int Urol Nephrol. 2008;40(2):443–51. https://doi.org/10.1007/s11255-008-9373-4.
20. Jeong HS, Dominguez AR. Calciphylaxis: controversies in pathogenesis, diagnosis and treatment. Am J Med Sci. 2016;351(2):217–27. https://doi.org/10.1016/j.amjms.2015.11.015.
21. Ghosh T, Winchester DS, Davis MDP, El-Azhary R, Comfere NI. Early clinical presentations and progression of calciphylaxis. Int J Dermatol. 2017;56(8):856–61. https://doi.org/10.1111/ijd.13622.
22. Weenig RH, Sewell LD, Davis MD, McCarthy JT, Pittelkow MR. Calciphylaxis: natural history, risk factor analysis, and outcome. J Am Acad Dermatol. 2007;56(4):569–79. https://doi.org/10.1016/j.jaad.2006.08.065.
23. Handa SP, Strzelczak D. Uremic small artery disease: calciphylaxis with penis involvement. Clin Nephrol. 1998;50(4):258–61.
24. Barbera V, Di Lullo L, Gorini A, Otranto G, Floccari F, Malaguti M, et al. Penile calciphylaxis in end stage renal disease. Case Rep Urol. 2013;2013:968916. https://doi.org/10.1155/2013/968916.
25. Kazanji N, Falatko J, Neupane S, Reddy G. Calciphylaxis presenting as digital ischemia. Intern Emerg Med. 2015;10(4):529–30. https://doi.org/10.1007/s11739-014-1172-6.
26. Wollina U. Update on cutaneous calciphylaxis. Indian J Dermatol. 2013;58(2):87–92. https://doi.org/10.4103/0019-5154.108026.
27. Wollina U. [Cutaneous calciphylaxis]. Der Hautarzt; Zeitschrift fur Dermatologie, Venerologie, und verwandte Gebiete. 2010;61(12):1063–71. https://doi.org/10.1007/s00105-010-2026-4 (**quiz 72**).
28. Nigwekar SU, Wolf M, Sterns RH, Hix JK. Calciphylaxis from nonuremic causes: a systematic review. Clin J Am Soc Nephrol. 2008;3(4):1139–43. https://doi.org/10.2215/CJN.00530108.
29. Reynolds JL, Joannides AJ, Skepper JN, McNair R, Schurgers LJ, Proudfoot D, et al. Human vascular smooth muscle cells undergo vesicle-mediated calcification in response to changes in extracellular calcium and phosphate concentrations: a potential mechanism for accelerated vascular calcification in ESRD. J Am Soc Nephrol. 2004;15(11):2857–67. https://doi.org/10.1097/01.ASN.0000141960.01035.28.
30. Weenig RH. Pathogenesis of calciphylaxis: Hans Selye to nuclear factor kappa-B. J Am Acad Dermatol. 2008;58(3):458–71. https://doi.org/10.1016/j.jaad.2007.12.006.
31. London GM, Guerin AP, Marchais SJ, Metivier F, Pannier B, Adda H. Arterial media calcification in end-stage renal disease:

impact on all-cause and cardiovascular mortality. Nephrol Dial Transpl. 2003;18(9):1731–40.
32. London GM, Marty C, Marchais SJ, Guerin AP, Metivier F, de Vernejoul MC. Arterial calcifications and bone histomorphometry in end-stage renal disease. J Am Soc Nephrol. 2004;15(7):1943–51.
33. Ishida M, Yao N, Yachiku S, Anzai T, Kobayashi T, Ishida H. Management of calcium, phosphorus and bone metabolism in dialysis patients using sevelamer hydrochloride and vitamin D therapy. Ther Apheresis Dial. 2005;9(Suppl 1):S16–21. https://doi.org/10.1111/j.1744-9987.2005.00325.x.
34. Moe SM, Chen NX. Mechanisms of vascular calcification in chronic kidney disease. J Am Soc Nephrol. 2008;19(2):213–6. https://doi.org/10.1681/ASN.2007080854.
35. Hayden MR, Tyagi SC, Kolb L, Sowers JR, Khanna R. Vascular ossification-calcification in metabolic syndrome, type 2 diabetes mellitus, chronic kidney disease, and calciphylaxis-calcific uremic arteriolopathy: the emerging role of sodium thiosulfate. Cardiovasc Diabetol. 2005;4:4. https://doi.org/10.1186/1475-2840-4-4.
36. Rogers NM, Teubner DJ, Coates PT. Calcific uremic arteriolopathy: advances in pathogenesis and treatment. Semin Dial. 2007;20(2):150–7. https://doi.org/10.1111/j.1525-139X.2007.00263.x.
37. Wozney JM, Rosen V, Celeste AJ, Mitsock LM, Whitters MJ, Kriz RW, et al. Novel regulators of bone formation: molecular clones and activities. Science. 1988;242(4885):1528–34.
38. Griethe W, Schmitt R, Jurgensen JS, Bachmann S, Eckardt KU, Schindler R. Bone morphogenic protein-4 expression in vascular lesions of calciphylaxis. J Nephrol. 2003;16(5):728–32.
39. Feng JQ, Xing L, Zhang JH, Zhao M, Horn D, Chan J, et al. NF-kappaB specifically activates BMP-2 gene expression in growth plate chondrocytes in vivo and in a chondrocyte cell line in vitro. J Biol Chem. 2003;278(31):29130–5. https://doi.org/10.1074/jbc.M212296200.
40. Kiechl S, Werner P, Knoflach M, Furtner M, Willeit J, Schett G. The osteoprotegerin/RANK/RANKL system: a bone key to vascular disease. Expert Rev Cardiovasc Ther. 2006;4(6):801–11. https://doi.org/10.1586/14779072.4.6.801.
41. Schafer C, Heiss A, Schwarz A, Westenfeld R, Ketteler M, Floege J, et al. The serum protein alpha 2-Heremans-Schmid glycoprotein/fetuin-A is a systemically acting inhibitor of ectopic calcification. J Clin Investig. 2003;112(3):357–66. https://doi.org/10.1172/JCI17202.
42. Wilmer WA, Magro CM. Calciphylaxis: emerging concepts in prevention, diagnosis, and treatment. Semin Dial. 2002;15(3):172–86.
43. Dahl PR, Winkelmann RK, Connolly SM. The vascular calcification-cutaneous necrosis syndrome. J Am Acad Dermatol. 1995;33(1):53–8.
44. Magro CM, Simman R, Jackson S. Calciphylaxis: a review. J Am Coll Certif Wound Spec. 2010;2(4):66–72. https://doi.org/10.1016/j.jcws.2011.03.001.
45. Mochel MC, Arakaki RY, Wang G, Kroshinsky D, Hoang MP. Cutaneous calciphylaxis: a retrospective histopathologic evaluation. Am J Dermatopathol. 2013;35(5):582–6. https://doi.org/10.1097/DAD.0b013e31827c7f5d.
46. Essary LR, Wick MR. Cutaneous calciphylaxis. An underrecognized clinicopathologic entity. Am J Clin Pathol. 2000;113(2):280–7. https://doi.org/10.1309/AGLF-X21H-Y37W-50KL.
47. Zembowicz A, Navarro P, Walters S, Lyle SR, Moschella SL, Miller D. Subcutaneous thrombotic vasculopathy syndrome: an ominous condition reminiscent of calciphylaxis: calciphylaxis sine calcifications? Am J Dermatopathol. 2011;33(8):796–802. https://doi.org/10.1097/DAD.0b013e31820edb81.
48. Beitz JM. Calciphylaxis: a case study with differential diagnosis. Ostomy Wound Manag. 2003;49(3):28–38 (**quiz 9–40**).
49. Nigwekar SU, Kroshinsky D, Nazarian RM, Goverman J, Malhotra R, Jackson VA, et al. Calciphylaxis: risk factors, diagnosis, and treatment. Am J Kidney Dis. 2015;66(1):133–46. https://doi.org/10.1053/j.ajkd.2015.01.034.
50. Brewster UC. Dermatological disease in patients with CKD. Am J Kidney Dis. 2008;51(2):331–44. https://doi.org/10.1053/j.ajkd.2007.09.024.
51. Sreedhar A, Sheikh HA, Scagliotti CJ, Nair R. Advanced-stage calciphylaxis: think before you punch. Clevel Clin J Med. 2016;83(8):562–4. https://doi.org/10.3949/ccjm.83a.15103.
52. Shmidt E, Murthy NS, Knudsen JM, Weenig RH, Jacobs MA, Starnes AM, 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. https://doi.org/10.1016/j.jaad.2012.05.037.
53. Han MM, Pang J, Shinkai K, Franc B, Hawkins R, Aparici CM. Calciphylaxis and bone scintigraphy: case report with histological confirmation and review of the literature. Ann Nucl Med. 2007;21(4):235–8. https://doi.org/10.1007/s12149-007-0013-3.
54. Norris B, Vaysman V, Line BR. Bone scintigraphy of calciphylaxis: a syndrome of vascular calcification and skin necrosis. Clin Nucl Med. 2005;30(11):725–7.
55. Martineau P, Pelletier-Galarneau M, Bazarjani S. The role of bone scintigraphy with single-photon emission computed tomography-computed tomography in the diagnosis and evaluation of calciphylaxis. World J Nuclear Med. 2017;16(2):172–4. https://doi.org/10.4103/1450-1147.203076.
56. 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. https://doi.org/10.1001/jamadermatol.2015.4591.
57. 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(2):186–90. https://doi.org/10.1016/j.jpainsymman.2006.03.009.
58. Poels M, Joppich R, Gerbershagen K, Wappler F. Analgesic therapy of calciphylaxis with levomethadone: a case study. Schmerz. 2010;24(6):621–4. https://doi.org/10.1007/s00482-010-0984-1.
59. Bechara FG, Altmeyer P, Kreuter A. Should we perform surgical debridement in calciphylaxis? Dermatol Surg. 2009;35(3):554–5. https://doi.org/10.1111/j.1524-4725.2009.01091.x.
60. Meissner M, Gille J, Kaufmann R. Calciphylaxis: no therapeutic concepts for a poorly understood syndrome? J German Soc Dermatol. 2006;4(12):1037–44. https://doi.org/10.1111/j.1610-0387.2006.06127.x.
61. O'Neil B, Southwick AW. Three cases of penile calciphylaxis: diagnosis, treatment strategies, and the role of sodium thiosulfate. Urology. 2012;80(1):5–8. https://doi.org/10.1016/j.urology.2012.04.012.
62. 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(7):444–50. https://doi.org/10.1111/nep.12433.
63. Tittelbach J, Graefe T, Wollina U. Painful ulcers in calciphylaxis—combined treatment with maggot therapy and oral pentoxyfillin. J Dermatol Treat. 2001;12(4):211–4. https://doi.org/10.1080/09546630152696035.
64. Wollina U, Helm C, Hansel G, Koch A, Schonlebe J, Haroske G, et al. Deep ulcer shaving combined with split-skin transplantation in distal calciphylaxis. Int J Lower Extrem Wounds. 2008;7(2):102–7. https://doi.org/10.1177/1534734608317891.
65. Arenas MD, Gil MT, Gutierrez MD, Malek T, Moledous A, Salinas A, et al. Management of calcific uremic arteriolopathy

(calciphylaxis) with a combination of treatments, including hyperbaric oxygen therapy. Clin Nephrol. 2008;70(3):261–4.
66. Banerjee C, Woller SC, Holm JR, Stevens SM, Lahey MJ. Atypical calciphylaxis in a patient receiving warfarin then resolving with cessation of warfarin and application of hyperbaric oxygen therapy. Clin Appl Thromb Hemost. 2010;16(3):345–50. https://doi.org/10.1177/1076029609355588.
67. Jull AB, Cullum N, Dumville JC, Westby MJ, Deshpande S, Walker N. Honey as a topical treatment for wounds. Cochrane Database Syst Rev. 2015(3):CD005083. https://doi.org/10.1002/14651858.cd005083.pub4.
68. McCallon SK, Weir D, Lantis JC 2nd. Optimizing wound bed preparation with collagenase enzymatic debridement. J Am Coll Clin Wound Spec. 2014;6(1–2):14–23. https://doi.org/10.1016/j.jccw.2015.08.003.
69. Vedvyas C, Winterfield LS, Vleugels RA. Calciphylaxis: a systematic review of existing and emerging therapies. J Am Acad Dermatol. 2012;67(6):e253–60. https://doi.org/10.1016/j.jaad.2011.06.009.
70. Peng T, Zhuo L, Wang Y, Jun M, Li G, Wang L, et al. A systematic review of sodium thiosulfate in treating calciphylaxis in chronic kidney disease patients. Nephrology. 2017. https://doi.org/10.1111/nep.13081.
71. Bourgeois P, De Haes P. Sodium thiosulfate as a treatment for calciphylaxis: a case series. J Dermatol Treat. 2016;27(6):520–4. https://doi.org/10.3109/09546634.2016.1163316.
72. Raymond CB, Wazny LD. Sodium thiosulfate, bisphosphonates, and cinacalcet for treatment of calciphylaxis. Am J Health Syst Pharm. 2008;65(15):1419–29. https://doi.org/10.2146/ajhp070546.
73. Noureddine L, Landis M, Patel N, Moe SM. Efficacy of sodium thiosulfate for the treatment for calciphylaxis. Clin Nephrol. 2011;75(6):485–90.
74. Singh RP, Derendorf H, Ross EA. Simulation-based sodium thiosulfate dosing strategies for the treatment of calciphylaxis. Clin J Am Soc Nephrol. 2011;6(5):1155–9. https://doi.org/10.2215/CJN.09671010.
75. Farese S, Stauffer E, Kalicki R, Hildebrandt T, Frey BM, Frey FJ, et al. Sodium thiosulfate pharmacokinetics in hemodialysis patients and healthy volunteers. Clin J Am Soc Nephrol. 2011;6(6):1447–55. https://doi.org/10.2215/CJN.10241110.
76. Auriemma M, Carbone A, Di Liberato L, Cupaiolo A, Caponio C, De Simone C, et al. Treatment of cutaneous calciphylaxis with sodium thiosulfate: two case reports and a review of the literature. Am J Clin Dermatol. 2011;12(5):339–46. https://doi.org/10.2165/11587060-000000000-00000.
77. Hackett BC, McAleer MA, Sheehan G, Powell FC, O'Donnell BF. Calciphylaxis in a patient with normal renal function: response to treatment with sodium thiosulfate. Clin Exp Dermatol. 2009;34(1):39–42. https://doi.org/10.1111/j.1365-2230.2008.02877.x.
78. Kalajian AH, Malhotra PS, Callen JP, Parker LP. Calciphylaxis with normal renal and parathyroid function: not as rare as previously believed. Arch Dermatol. 2009;145(4):451–8. https://doi.org/10.1001/archdermatol.2008.602.
79. Sanguankeo A, Thamcharoen N, Upala S. Calciphylaxis in a nondialysis patient treated with sodium thiosulfate and high dose of oxygen. Clin Nephrol Case Stud. 2017;5:38–41. https://doi.org/10.5414/CNCS108959.
80. Schlieper G, Brandenburg V, Ketteler M, Floege J. Sodium thiosulfate in the treatment of calcific uremic arteriolopathy. Nat Rev Nephrol. 2009;5(9):539–43. https://doi.org/10.1038/nrneph.2009.99.
81. Selk N, Rodby RA. Unexpectedly severe metabolic acidosis associated with sodium thiosulfate therapy in a patient with calcific uremic arteriolopathy. Semin Dial. 2011;24(1):85–8. https://doi.org/10.1111/j.1525-139X.2011.00848.x.
82. Strazzula L, Nigwekar SU, Steele D, Tsiaras W, Sise M, Bis S, et al. Intralesional sodium thiosulfate for the treatment of calciphylaxis. JAMA Dermatol. 2013;149(8):946–9. https://doi.org/10.1001/jamadermatol.2013.4565.
83. Ossorio-Garcia L, Jimenez-Gallo D, Arjona-Aguilera C, Linares-Barrios M. Intralesional sodium thiosulfate to treat calciphylaxis. Actas Dermosifiliogr. 2016;107(4):359–62. https://doi.org/10.1016/j.ad.2015.10.013.
84. Isoherranen K, Bouchard L, Kluger N. Benefits of intralesional injections of sodium thiosulfate in the treatment of calciphylaxis. Int Wound J. 2017. https://doi.org/10.1111/iwj.12738.
85. Malabu UH, Manickam V, Kan G, Doherty SL, Sangla KS. Calcific uremic arteriolopathy on multimodal combination therapy: still unmet goal. Int J Nephrol. 2012;2012:390768. https://doi.org/10.1155/2012/390768.
86. Nigwekar SU, Sprague SM. We do too many parathyroidectomies for calciphylaxis. Semin Dial. 2016;29(4):312–4. https://doi.org/10.1111/sdi.12502.
87. Rroji M, Spasovski G. Calcimimetics versus parathyroidectomy: what is preferable? Int Urol Nephrol. 2018. https://doi.org/10.1007/s11255-018-1838-5.
88. Hull R, Delmore T, Carter C, Hirsh J, Genton E, Gent M, et al. Adjusted subcutaneous heparin versus warfarin sodium in the long-term treatment of venous thrombosis. N Engl J Med. 1982;306(4):189–94. https://doi.org/10.1056/NEJM198201283060401.
89. Pautas E, Gouin I, Bellot O, Andreux JP, Siguret V. Safety profile of tinzaparin administered once daily at a standard curative dose in two hundred very elderly patients. Drug Saf. 2002;25(10):725–33.
90. el-Azhary RA, Arthur AK, Davis MD, McEvoy MT, Gibson LE, Weaver AL et al. Retrospective analysis of tissue plasminogen activator as an adjuvant treatment for calciphylaxis. JAMA Dermatol. 2013;149(1):63–7. https://doi.org/10.1001/2013.jamadermatol.5.
91. Sewell LD, Weenig RH, Davis MD, McEvoy MT, Pittelkow MR. Low-dose tissue plasminogen activator for calciphylaxis. Arch Dermatol. 2004;140(9):1045–8. https://doi.org/10.1001/archderm.140.9.1045.
92. Bhat S, Hegde S, Bellovich K, El-Ghoroury M. Complete resolution of calciphylaxis after kidney transplantation. Am J Kidney Dis. 2013;62(1):132–4. https://doi.org/10.1053/j.ajkd.2012.12.029.
93. Vanbelleghem H, Terryn W, Van Leuven L, Van Caesbroeck D, Demetter P, Lameire N. A dramatic case of calciphylaxis 20 years after kidney transplantation. Nephrol Dial Transpl. 2004;19(12):3183–5. https://doi.org/10.1093/ndt/gfh442.
94. Mohammed IA, Sekar V, Bubtana AJ, Mitra S, Hutchison AJ. Proximal calciphylaxis treated with calcimimetic 'cinacalcet'. Nephrol Dial Transpl. 2008;23(1):387–9. https://doi.org/10.1093/ndt/gfm676.
95. Ross EA. Evolution of treatment strategies for calciphylaxis. Am J Nephrol. 2011;34(5):460–7. https://doi.org/10.1159/000332221.
96. Fine A, Zacharias J. Calciphylaxis is usually non-ulcerating: risk factors, outcome and therapy. Kidney Int. 2002;61(6):2210–7. https://doi.org/10.1046/j.1523-1755.2002.00375.x.
97. Lal G, Nowell AG, Liao J, Sugg SL, Weigel RJ, Howe JR. Determinants of survival in patients with calciphylaxis: a multivariate analysis. Surgery. 2009;146(6):1028–34. https://doi.org/10.1016/j.surg.2009.09.022.