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NDT Perspectives

Lack of evidence does not justify neglect: how can we address unmet medical needs in calciphylaxis?

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ABSTRACT

Calcific uraemic arteriolopathy (CUA), or calciphylaxis, is a rare disease predominantly occurring in comorbidity with dialysis. Due to the very low frequency of CUA, prospective studies on its management are lacking and even anecdotal reports on treatment remain scarce. Therefore, calciphylaxis is still a challenging disease with dismal prognosis urgently requiring adequate strategies for diagnosis and treatment.

In an attempt to fill some of the current gaps in evidence on various, highly debated and controversial aspects of dialysis-associated calciphylaxis, 13 international experts joined the 1st Consensus Conference on CUA, held in Leuven, Belgium on 21 September 2015. The conference was supported by the European Calciphylaxis Network (EuCalNet), which is a task force of the ERA-EDTA scientific working group on Chronic Kidney Disease—Mineral and Bone Disorders (CKD-MBD). After an intense discussion, a 9-point Likert scale questionnaire regarding 20 items on calciphylaxis was anonymously answered by each participant. These 20 items addressed unsolved issues in terms of diagnosis and management of calciphylaxis. On the one hand, the analysis of the expert opinions identified areas of general consensus, which might be a valuable aid for physicians treating such a disease with less experience in the field. On the other hand, some topics such as the pertinence of skin biopsy and administration of certain treatments revealed divergent opinions. The aim of the present summary report is to provide some guidance for clinicians who face patients with calciphylaxis in the current setting of absence of evidence-based medicine.

Keywords: calciphylaxis, cardiovascular, chronic renal failure, CKD-MBD, mineral metabolism

INTRODUCTION

Calcific uraemic arteriolopathy (CUA), or calciphylaxis, is a rare devastating syndrome (Orphanet number ORPHA280062) characterized by progressive and painful skin ulcerations associated with media calcification of small- and medium-size vessels in the dermis and subcutaneous tissue. It has an estimated incidence of <1% among dialysis patients [1], who are the predominantly affected patient cohort [2]. Currently, due to the paucity of evidence from randomized controlled trials (RCTs), no standard treatment is available and patient management is primarily based on physicians' clinical experience and anecdotal reports. As a consequence, calciphylaxis in patients on dialysis remains a life-threatening condition with unmet clinical needs, urgently requiring adequate diagnosis and treatment strategies.

Thirteen international experts in the field of calciphylaxis, belonging to the areas of nephrology, cardiology and biochemistry and all listed as authors, joined the 1st Consensus Conference on CUA, held in Leuven, Belgium on 21 September 2015, supported by the European Calciphylaxis Network (EuCalNet), which is a Task Force of the European Renal Association—European Dialysis and Transplant Association (ERA-EDTA) scientific working group on Chronic Kidney Disease—Mineral and Bone Disorders (CKD-MBD). Various issues were addressed, covering aspects related to dialysis-associated CUA prevention, pathophysiology, diagnosis and treatment. Following presentations by each expert on these particular topics of expertise, an intensive discussion was started in an attempt to reach a consensus on the standards for CUA diagnosis and therapy. In order to evaluate each expert's opinion, a 9-point Likert scale questionnaire [3] (1, 'strong disagreement'–9, 'strong agreement') was distributed at the end of the discussion that comprised 20 items related to different aspects of calciphylaxis in dialysis patients. The items addressed were selected based on their clinical relevance, but also on the group's personal experience. Hence, not all of the aspects of potential interest in the field were covered (e.g. hyperbaric oxygen therapy did not turn out to be part of routine calciphylaxis treatment in the involved centres). A score of 1–3 inferred 'disagreement', 4–6 'undecided/neutral' and 7–9 'agreement'. Answers were anonymous and results were summarized graphically, with the median score and the interquartile (Q1–Q3) range. L.J.S., as a non-physician, did not participate in the vote.

In the following paragraphs, each item is reported along with the corresponding graph and a brief comment including a summary of the rationale justifying the experts' answers.

ITEM 1

Performing a biopsy is a prerequisite for diagnosing CUA *(median 4.5; Q1–Q3 range 2–7)*

The experts' opinions vary from strong disagreement to strong agreement (Figure 1A). The heterogeneous pattern of the answers reflects the current debate on the role of skin biopsy to confirm the diagnosis of calciphylaxis. Often the clinical picture is clear enough even without a biopsy, as the presence of painful lesions and the association with advanced renal disease and other possible risk factors raises a high suspicion of calciphylaxis. Dermal induration upon palpation ('leather-like') is typical. Certainly skin biopsy is a useful tool in the workup of the disease to exclude other conditions that can mimic it, and thus to establish a definitive diagnosis [4, 5]. However, concerns have been raised on the possibility that punch skin biopsy may induce ulceration and worsen the disease course through superimposed infections, bleeding and induction of new areas of necrosis [6]. Obviously, skin biopsy is a requirement for research purposes. In summary, skin biopsy is not a prerequisite for establishing the diagnosis and should be limited to ambiguous cases.

ITEM 2

The clinical picture is sufficient to diagnose CUA in most cases *(median 7; Q1–Q3 range 2–8)*

The majority of experts [8/12 (67%)] agreed with this statement, whereas others [4/12 (33%)] expressed disagreement (Figure 1B). Indeed, although the degree of cutaneous and subcutaneous tissue involvement is highly variable, superficial pain is virtually always part of the initial clinical picture. Moreover, the association with advanced renal disease as well as the palpation of firm calcified subcutaneous tissue is suggestive of the diagnosis of calciphylaxis [4, 5].

ITEM 3

There are a high number of missed, undiagnosed cases *(median 8; Q1–Q3 range 6–9)*

Most of the experts [9/12 (75%)] agreed that a potentially high number of cases are missed (Figure 1C). This is due to the fact that CUA is a rare disease and awareness might be suboptimal among caregivers [4, 5]. The exact number of hidden cases, especially regarding minor or abortive forms, remains speculative. The identification of minor or abortive stages of calciphylaxis might be associated with improved outcome in case therapy is started early rather than late after the development of the full-blown clinical picture.

ITEM 4

CUA is a homogeneous disease irrespective of the nature and the distribution of skin lesions *(median 2.5; Q1–Q3 range 1.5–3)*

The experts almost uniformly [10/12 (83%)] expressed disagreement (Figure 1D), indicating a strong trend towards the opinion that calciphylaxis is a heterogeneous disease. In fact, the severe painful skin lesions at first presentation may be of different types (i.e. livedo reticularis, reticulate purpura, violaceous plaques or indurated nodules). Some patients with calciphylaxis never develop ulcerations, while in others such ulcers dominate the clinical picture from the early phases. The anatomical distribution and comorbidities vary remarkably between a

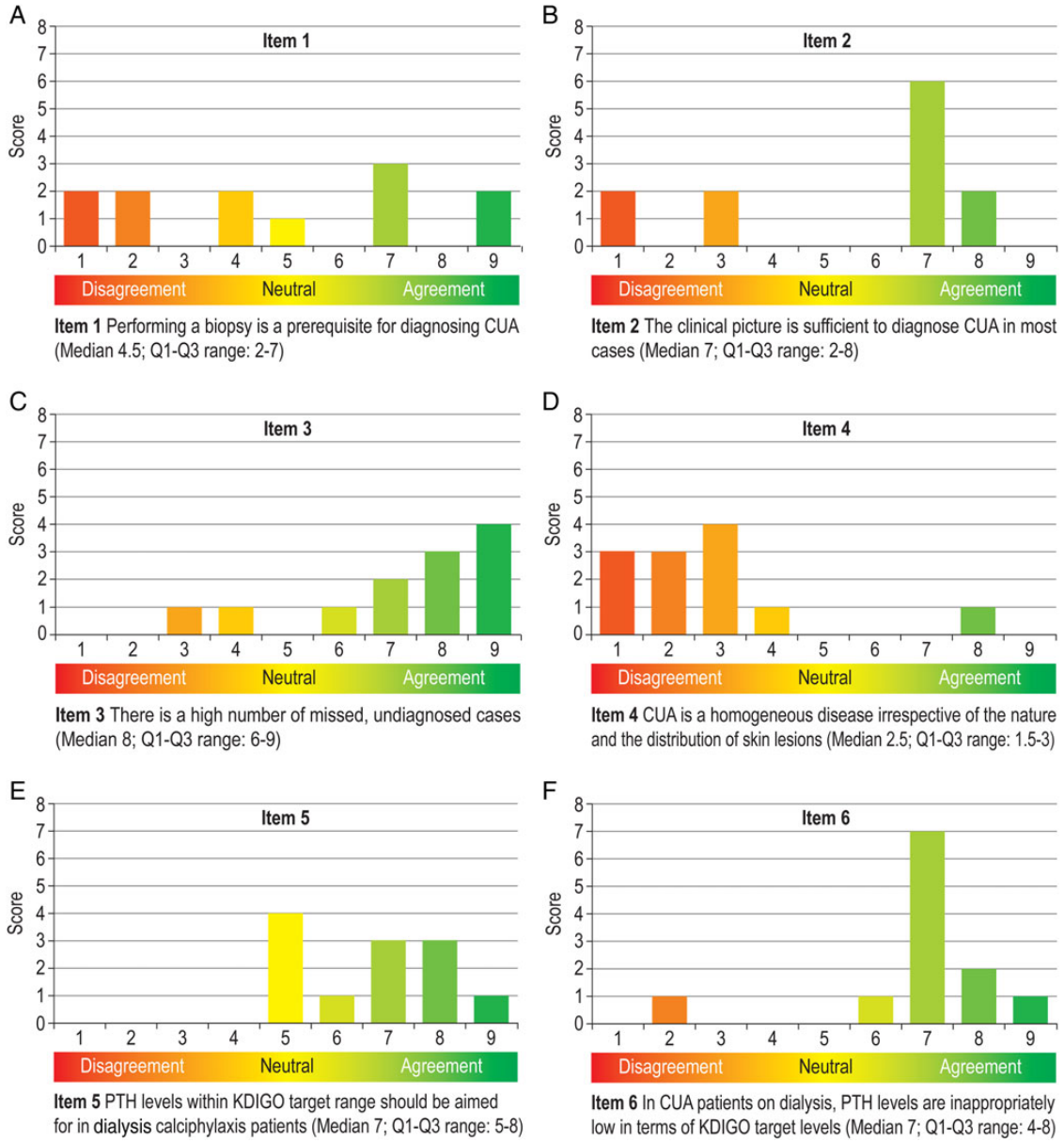


FIGURE 1: Illustration of answers to items 1 to 6 of the questionnaire.

peripheral and a central form (abdominal and gluteal region) [1, 4]. Overall, the experts consented that reliable diagnostic criteria for calciphylaxis need to be established.

ITEM 5

Parathyroid hormone (PTH) levels within the Kidney Disease: Improving Global Outcomes (KDIGO) target range should be aimed for in dialysis calciphylaxis patients *(median 7; Q1–Q3 range 5–8)*

The majority of experts agreed with this statement [7/12 (58%)], whereas the remainder [5/12 (42%)] were unsure (Figure 1E). However, in clinical practice, it is particularly difficult to achieve an increase of low serum PTH levels (i.e. below the KDIGO target range), which potentially reflect low-turnover bone disease or adynamic bone disease (ABD) as one possible trigger for CUA [2]. Conversely, it is relatively easy to bring excessively high PTH levels back to the KDIGO target range.

ITEM 6

In CUA patients on dialysis, PTH levels are inappropriately low in terms of KDIGO target levels *(median 7; Q1–Q3 range 4–8)*

Overall, the expert opinion is in agreement [10/12 (83%)] with the statement that the levels of circulating PTH are inappropriately low (Figure 1F) compared with the PTH target recommended by KDIGO [6], which suggests a target range for PTH between two and nine times the upper limit of the normal reference range for the assay used (~130–600 pg/mL).

Indeed, data emerging from the German calciphylaxis registry (2006–15) clearly showed that a high proportion of calciphylaxis patients on dialysis had PTH levels <130 pg/mL, indicative of a low-turnover bone disease [2].

ITEM 7

A defect in calcification-inhibitory potency is a prerequisite *(median 6; Q1–Q3 range 3.5–8)*

Although the answers distribute along the scale, the general opinion is slightly shifted towards agreement, as 50% of experts agreed with this item (Figure 2A) whereas the remaining 50% expressed disagreement. This is due to the fact that available data point towards the imbalance between calcification promoters and inhibitors as a leading factor in extraosseous calcification in CKD rather than just inhibitors. Indeed, preclinical and clinical studies have shown the involvement of a plethora of factors, both systemic circulating and local, that may act differently on different parts of the arterial tree in the development of unwanted calcification processes in the body [7]. Notably, the discovery of these mechanisms has led to the development of specific interventions aimed at promoting a new balance between pro- and anti-calcifying factors [1]. Among inhibitors, the current focus is on matrix Gla protein (MGP), a protein exclusively expressed in vascular smooth muscle cells and chondrocytes. To be fully active, MGP requires post-translational phosphorylation and vitamin K–dependent gamma-carboxylation; accordingly, warfarin treatment suppresses MGP activation [8].

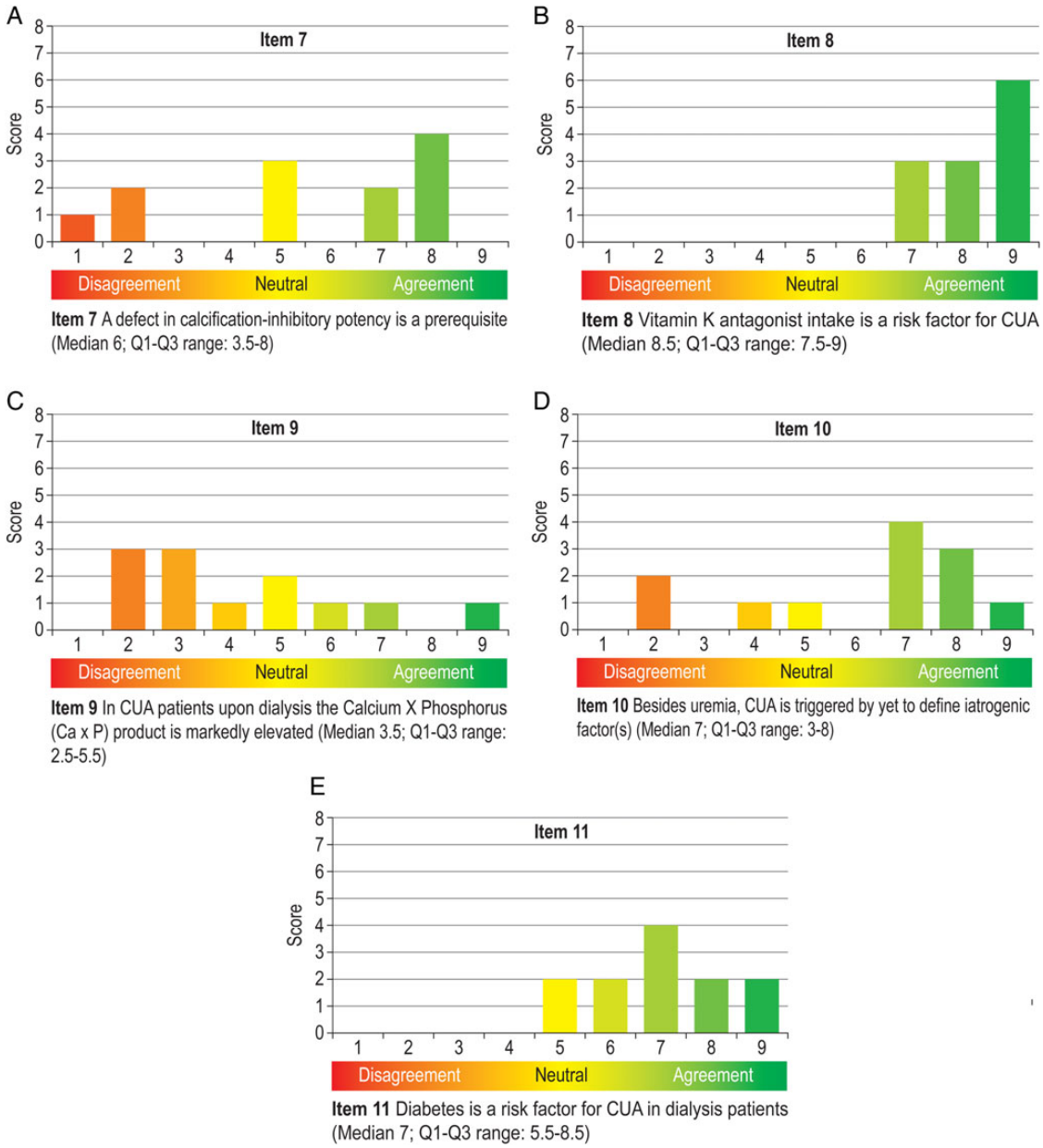


FIGURE 2: Illustration of answers to items 7 to 11 of the questionnaire.

ITEM 8

Vitamin K antagonist intake is a risk factor for CUA *(median 8.5; Q1–Q3 range 7.5–9)*

The experts fully (100%) agreed that the use of vitamin K antagonists (VKAs) increases the risk of CUA (Figure 2B). Although clear evidence from prospective clinical trials is lacking, *in vitro*, *in vivo* and human cohort studies have shown that the use of VKAs such as warfarin accelerates cardiovascular calcification [8–10] and increases the risk of calciphylaxis [11, 12]. Biochemically, one possible explanation resides in the key role of vitamin K–dependent post-translational modifications required for the activation of the calcification inhibitor MGP (see Item 5). A recent report from Delanaye *et al.* [13] showed that stopping VKA in seven haemodialysis (HD) patients led to a rapid and significant reduction of inactive MGP levels, although no data are available yet on the effect of this reduction on vascular calcification or on calciphylaxis outcomes.

ITEM 9

In CUA patients on dialysis the calcium × phosphorus (Ca × P) product is markedly elevated *(median 3.5; Q1–Q3 range 2.5–5.5)*

Although the experts' answers are spread along the scale, the overall opinion is slightly shifted towards disagreement [6/12 (50%)] (Figure 2C). The rationale behind this answer is that an increased level of circulating Ca × P product has been shown to be a predictor of cardiovascular risk and calcification in the majority of dialysis patients, and a risk factor for calciphylaxis [14, 15]. On the other hand, various reports have demonstrated that many cases have occurred in the presence of apparently low or normal serum Ca levels [2]. In fact, a normal Ca × P product may result from an impaired capacity of serum to keep Ca and P ions in solution, leading to a rapid deposition of Ca and P within extraosseous calcifications [16]. Overall, the experts agreed that overt (constant) hypercalcaemia is not a prerequisite for calciphylaxis. Previous data from the German calciphylaxis registry indicated that CKD-MBD parameters are highly variable in calciphylaxis patients [2].

ITEM 10

Besides the uraemic state, CUA is triggered by as yet to be defined iatrogenic factors *(median 7; Q1–Q3 range 3–8)*

The majority of experts [7/12 (67%)] agreed with this item, whereas the remainder equally expressed uncertainty [2/12 (17%)] or disagreement [2/12 (17%)] (Figure 2D). Indeed, in contrast to hypertension or anaemia, calciphylaxis is not an issue of previously unrecognized or neglected CKD. Virtually all patients with CUA have been regularly monitored for a long period of time and develop CUA despite intensive surveillance.

ITEM 11

Diabetes is a risk factor for CUA in dialysis patients *(median 7; Q1–Q3 range 5.5–8.5)*

The majority of experts [8/12 (67%)] agreed with this item, whereas the remainder [4/12 (33%)] were undecided (Figure 2E). The rationale behind this result resides in the observation that diabetes is a frequent comorbidity in CUA patients and it is not a condition *sine qua non*. Moreover, the association between calciphylaxis and diabetes, just like all the other risk factors, has not been rigorously studied to confirm causality, and data come from studies suffering from limitations such as small sample size and single-centre experience [1, 17]. Finally, no data are available regarding whether diabetes control or duration affects calciphylaxis risk [17].

ITEM 12

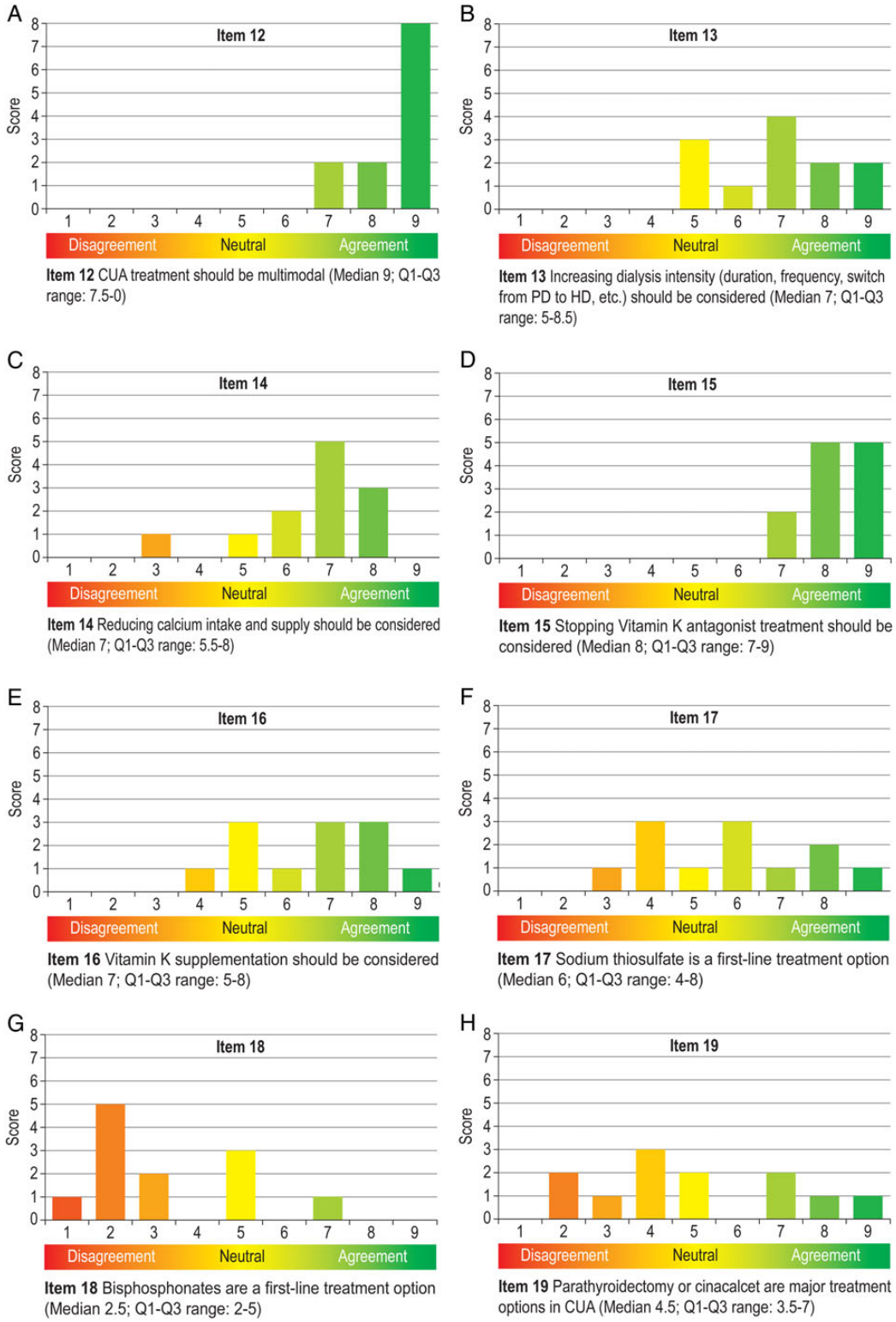
CUA treatment should be multimodal *(median 9; Q1–Q3 range 7.5–9)*

The experts unanimously agreed with the statement that treatment of CUA should be multimodal (Figure 3A). Such a multimodal approach has been previously recommended [1, 17]. Multimodality has been reported to be associated with successful CUA resolution [5, 17, 18], although patients should be carefully evaluated on a case-by-case basis. Overall, the discovery of a single magic bullet for CUA treatment is unlikely.

ITEM 13

Increasing dialysis intensity [duration, frequency, switch from peritoneal dialysis (PD) to HD, etc.] should be considered *(median 7; Q1–Q3 range 5–8.5)*

Most of the experts [8/12 (67%)] agreed with the statement that intensifying dialysis should be taken into consideration, whereas the remainder [4/12 (33%)] were unsure (Figure 3B). In general, due to the lack of clear evidence on any of the proposed interventions to better control CUA, treatment recommendations are largely based on clinical experience and results from observational studies. The aim of dialysis intensification, possibly through increased length and frequency, or switching from HD to hemodiafiltration (HDF) or from PD to HD or HDF, is to enhance calcium and phosphate removal. Notably, intensifying HD has been recommended by Baldwin *et al.* [18], whereas concerns have been raised on the use of PD, as it may confer higher calciphylaxis risk. The reason for the increased CUA incidence among PD patients remains unclear, but one possibility is the use of calcium-containing phosphate binders. The switch from PD and HD may actually be beneficial for calciphylaxis patients [19].



Item 12 CUA treatment should be multimodal (Median 9; Q1-Q3 range: 7.5-0)

Item 13 Increasing dialysis intensity (duration, frequency, switch from PD to HD, etc.) should be considered (Median 7; Q1-Q3 range: 5-8.5)

Item 14 Reducing calcium intake and supply should be considered (Median 7; Q1-Q3 range: 5.5-8)

Item 15 Stopping Vitamin K antagonist treatment should be considered (Median 8; Q1-Q3 range: 7-9)

Item 16 Vitamin K supplementation should be considered (Median 7; Q1-Q3 range: 5-8)

Item 17 Sodium thiosulfate is a first-line treatment option (Median 6; Q1-Q3 range: 4-8)

Item 18 Bisphosphonates are a first-line treatment option (Median 2.5; Q1-Q3 range: 2-5)

Item 19 Parathyroidectomy or cinacalcet are major treatment options in CUA (Median 4.5; Q1-Q3 range: 3.5-7)

FIGURE 3: Illustration of answers to items 12 to 19 of the questionnaire.

ITEM 14

Reducing calcium intake and supply should be considered *(median 7; Q1–Q3 range 5.5–8)*

The overall opinion is of agreement [8/12 (67%)] with this item (Figure 3C). It is well established that, together with phosphate, calcium is the main component of vascular calcifications. However, relatively normal or even low serum calcium levels are possible at the time of calciphylaxis diagnosis, due to its tissue deposition. Fine and Fontaine [19] reported that after reducing the amount of calcium salts given to dialysis patients (mostly PD), the incidence of CUA significantly decreased over several years in their dialysis centre.

ITEM 15

Stopping vitamin K antagonist treatment should be considered *(median 8; Q1–Q3 range 7–9)*

The experts expressed complete agreement with this statement (Figure 3D). Indeed, compelling evidence has shown that VKA treatment is a risk factor for calciphylaxis (see Item 7) [2]. Ongoing VKA prescription should be limited to very few CUA cases, such as patients with mitral prosthetic heart valve replacement.

ITEM 16

Vitamin K supplementation should be considered *(median 7; Q1–Q3 range 5–8)*

The majority of experts [7/12 (58%)] agreed with this item, whereas the remainder were unsure [5/12 (42%)] (Figure 3E). As already stated lessons learned from *in vitro* and *in vivo* studies highlight the key role of vitamin K in protecting from and possibly reverting vascular calcifications [8, 10, 20]. Moreover, it has been recently demonstrated that most dialysis patients exhibit pronounced vitamin K deficiency and that supplementation with vitamin K2 in HD patients can markedly decrease the levels of inactive MGP in a dose-dependent fashion [21, 22]. However, more data from RCTs are needed to understand whether supplementation of vitamin K may be of benefit for the cardiovascular health of patients [23]. According to the expert discussion, it seems that there is no clear rationale for preferring K2 (menaquinone-7) over K1 supplementation. Vitamin K application in CKD patients was regarded as being generally safe by the experts.

ITEM 17

Sodium thiosulfate is a first-line treatment option *(median 6; Q1–Q3 range 4–8)*

The experts expressed heterogeneous opinions with regard to this item, as 58% (7/12) were uncertain, 33% (4/12) agreed and 1 expert disagreed (Figure 3F). Sodium thiosulfate (STS) has been available as a chelating agent indicated for the treatment of cyanide intoxication; as an off-label indication, however, it is a common intervention used to treat calciphylaxis. STS has been used in calciphylaxis patients, often as part of a multimodal approach, resulting in clinical improvements [24–26] including a reduction in pain. Yet, a definitive conclusion on the efficacy and safety of STS cannot be drawn, since prospective controlled data are missing. Moreover, a publication bias favouring positive results cannot be excluded. Concerns exist about the duration of therapy with STS, the dose, the method of administration and the cost, which may affect the choice and duration of this drug as a feasible option for these patients [1]. Potential side effects such as induction of metabolic acidosis and bone demineralization warrant attention.

ITEM 18

Bisphosphonates are a first-line treatment option *(median 2.5; Q1–Q3 range 2–5)*

Most of the experts expressed disagreement [8/12 (67%)] with this item, whereas 1 expert agreed and the remaining 3 were undecided (Figure 3G). It is unclear whether they interact with extraosseous calcification processes via their antiresorptive bone effects or via direct peripheral pyrophosphate-like effects at the tissue sites. Published data are scarce, and mostly from case reports and case series [27, 28], and therefore the routine use of this molecules is not indicated. Moreover, as they may worsen ABD, especially in patients with stage 4–5D CKD, their use should be considered only in selected cases in which ABD is excluded or highly unlikely.

ITEM 19

Parathyroidectomy or cinacalcet are major treatment options in CUA *(median 4.5; Q1–Q3 range 3.5–7)*

The experts' opinions are dispersed between disagreement and agreement, but 42% (5/12) expressed uncertainty (Figure 3H). The choice of parathyroidectomy or cinacalcet strongly depends on the patient's characteristics and therefore their use must be carefully evaluated for each individual patient. In calciphylaxis patients with overt hyperparathyroidism and signs of high bone turnover, 'emergency' parathyroidectomy should be considered. The EVOLVE trial ($n = 3861$ dialysis patients) investigated the occurrence of calciphylaxis with respect to cinacalcet compared with placebo treatment [29]. Of note, in EVOLVE the median PTH levels prior to CUA development were 796 pg/mL in the placebo arm ($n = 18$ cases) and 410 pg/mL in the cinacalcet arm ($n = 6$ cases) [29]. The unadjusted relative hazard was 0.31 (95% CI 0.13–0.79; P = 0.014). Importantly, the EVOLVE study included preselected dialysis patients with advanced hyperparathyroidism at baseline, while a nationwide approach such as the German registry [2] is unlimited by any exclusion criteria. So the EVOLVE cohort is presumably not representative regarding the predominant PTH range for calciphylaxis development and at the same time fuels speculation about an optimal intermediate (protective) PTH range.

ITEM 20

Prognosis of CUA is poor *(median 8.5; Q1–Q3 range 7.5–9)*

The experts evenly agreed that, to date, CUA prognosis remains dismal (Figure 4). In fact, it is associated with high morbidity, mostly depending on infections and cardiovascular disorders, and a mortality of up to 80%, likely due to infections of necrotic skin resulting in sepsis [30]. Lessons from clinical experience have shown that patients with large ulcerative skin lesions carry the worst prognosis, particularly based on the infectious risk due to the destroyed skin barrier.

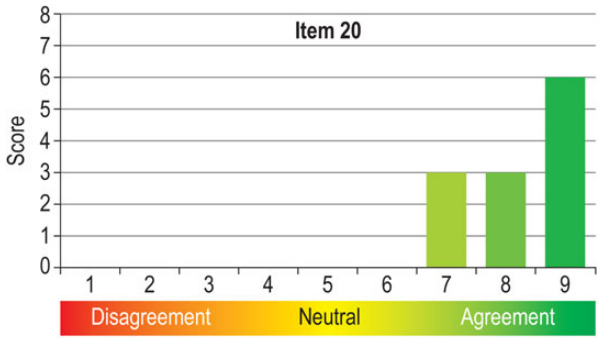


FIGURE 4: Illustration of answers to item 20 of the questionnaire.

CONCLUSIONS

What emerges from the experts' answers is that a general consensus actually exists on specific issues related to calciphylaxis diagnosis, risk factors and treatment strategies, although based mainly on daily practice experience and observational studies rather than on clear evidence from RCTs. Nevertheless, the present article cannot cover all aspects of calciphylaxis and the experts acknowledge the presence of some topics that remain the objective of an open debate, such as whether it is appropriate to perform skin biopsy at the time of diagnosis or to administer certain treatments to dialysis patients with calciphylaxis (e.g. hyperbaric oxygen therapy or statins), therefore highlighting major targets for future research efforts.

CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest regarding the conception of the meeting, data collection and analysis as well as data presentation in this article. We declare that the results presented here, in whole or part, have not been published previously.

REFERENCES

1. Brandenburg VM, Cozzolino M, Mazzaferro S. Calcific uremic arteriolopathy: a call for action. Semin Nephrol 2014; 34: 641–647
2. Brandenburg V, Kramann R, Rothe H *et al.* Calcific uremic arteriolopathy (calciphylaxis): data from a large nation-wide registry. Nephrol Dial Transplant 2016; doi: 10.1093/ndt/gfv438.
3. Likert R. A technique for the measurement of attitudes. Arch Psychol 1932; 140: 1–55
4. Brandenburg VM, Cozzolino M, Ketteler M. Calciphylaxis: a still unmet challenge. J Nephrol 2011; 24: 142–148
5. Nigwekar SU, Kroshinsky D, Nazarian RM *et al.* Calciphylaxis: risk factors, diagnosis, and treatment. Am J Kidney Dis 2015; 66: 133–146
6. Kidney Disease: Improving Global Outcomes CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder. (CKD-MBD). Kidney Int Suppl 2009; 113: S1–S130
7. Schlieper G, Schurgers L, Brandenburg V *et al.* Vascular calcification in chronic kidney disease: an update. Nephrol Dial Transplant 2016; 31: 31–39
8. Schurgers LJ, Spronk HMH, Skepper JN *et al.* Post-translational modifications regulate matrix Gla protein function: importance for inhibition of vascular smooth muscle cell calcification. J Thromb Haemost 2007; 5: 2503–2511
9. Krüger T, Oelenberg S, Kaesler N *et al.* Warfarin induces cardiovascular damage in mice. Arterioscler Thromb Vasc Biol 2013; 33: 2618–2624
10. Schurgers LJ, Spronk HMH, Soute BAM *et al.* Regression of warfarin-induced medial elastocalcinosis by high intake of vitamin K in rats. Blood 2007; 109: 2823–2831
11. Hayashi M, Takamatsu I, Kanno Y *et al.* A case-control study of calciphylaxis in Japanese end-stage renal disease patients. Nephrol Dial Transplant 2012; 27: 1580–1584
12. Nigwekar SU, Bhan I, Turchin A *et al.* Statin use and calcific uremic arteriolopathy: a matched case-control study. Am J Nephrol 2013; 37: 325–332
13. Delanaye P, Dubois BE, Lukas P *et al.* Impact of stopping vitamin K antagonist therapy on concentrations of dephospho-uncarboxylated matrix Gla protein. Clin Chem Lab Med 2015; 53: e191–e193
14. Floege J. When man turns to stone: extraosseous calcification in uremic patients. Kidney Int 2004; 65: 2447–2462
15. Cozzolino M, Staniforth ME, Liapis H *et al.* Sevelamer hydrochloride attenuates kidney and cardiovascular calcifications in long-term experimental uremia. Kidney Int 2003; 64: 1653–1661
16. Ketteler M, Brandenburg V, Jahnen-Dechent W *et al.* Do not be misguided by guidelines: the calcium × phosphate product can be a Trojan horse. Nephrol Dial Transplant 2005; 20: 673–677
17. Nigwekar SU. Multidisciplinary approach to calcific uremic arteriolopathy. Curr Opin Nephrol Hypertens 2015; 24: 531–537
18. Baldwin C, Farah M, Leung M *et al.* Multi-intervention management of calciphylaxis: a report of 7 cases. Am J Kidney Dis 2011; 58: 988–991
19. Fine A, Fontaine B. Calciphylaxis: the beginning of the end? Perit Dial Int. 2008; 28: 268–270
20. Hale JE, Williamson MK, Price PA. Carboxyl-terminal proteolytic processing of matrix Gla protein. J Biol Chem 1991; 266: 21145–21149
21. Westenfeld R, Krueger T, Schlieper G *et al.* Effect of vitamin K2 supplementation on functional vitamin K deficiency in hemodialysis patients: a randomized trial. Am J Kidney Dis 2012; 59: 186–195
22. Caluwé R, Vandecasteele S, Van Vlem B *et al.* Vitamin K2 supplementation in haemodialysis patients: a randomized dose-finding study. Nephrol Dial Transplant 2014; 29: 1385–1390
23. Brandenburg VM, Schurgers LJ, Kaesler N *et al.* Prevention of vasculopathy by vitamin K supplementation: can we turn fiction into fact? Atherosclerosis 2015; 240: 10–16
24. Zitt E, König M, Vychytil A *et al.* Use of sodium thiosulphate in a multiinterventional setting for the treatment of calciphylaxis in dialysis patients. Nephrol Dial Transplant 2013; 28: 1232–1240
25. Strazzula L, Nigwekar SU, Steele D *et al.* Intralesional sodium thiosulfate for the treatment of calciphylaxis. JAMA Dermatol 2013; 149: 946–949
26. Nigwekar SU, Brunelli SM, Meade D *et al.* Sodium thiosulfate therapy for calcific uremic arteriolopathy. Clin J Am Soc Nephrol 2013; 8: 1162–1170
27. Torregrosa J-V, Sánchez-Escuredo A, Barros X *et al.* Clinical management of calcific uremic arteriolopathy before and after therapeutic inclusion of bisphosphonates. Clin Nephrol 2015; 83: 231–234
28. da Costa JB, da Costa AG, Gomes MM. Pamidronate as a treatment option in calciphylaxis. J Eur Acad Dermatol Venereol 2008; 22: 1128–1130
29. Floege J, Kubo Y, Floege A. *et al.* The effect of cinacalcet on calcific uremic arteriolopathy events in patients receiving hemodialysis: the EVOLVE trial. Clin J Am Soc Nephrol 2015; 10: 800–807
30. Weenig RH, Sewell LD, Davis MDP *et al.* Calciphylaxis: natural history, risk factor analysis, and outcome. J Am Acad Dermatol 2007; 56: 569–579

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