Received: 14 July 2022 | Revised: 24 October 2022 | Accepted: 20 January 2023

DOI: 10.1111/hdi.13071

SPECIAL ARTICLE

Miscellaneous

Chronic kidney disease-associated pruritus in patients undergoing hemodialysis: Xerosis and topical therapy

Arum Krismi[1,2] | **Retno Danarti**[3] | **Ida I. Dewa Putu Pramantara Setiabudi**[4] | **Yohanes W. Wirohadidjojo**[3]

[1]Doctoral Study of Medicine and Health, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia

[2]Faculty of Medicine, Duta Wacana Christian University, Yogyakarta, Indonesia

[3]Department of Dermatology and Venereology, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia

[4]Department of Internal Medicine/Geriatry, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia

Correspondence
Arum Krismi, Faculty of Medicine, Duta Wacana Christian University, Jl. Dr. Wahidin Sudirohusodo no. 5-25, Yogyakarta 55224, Indonesia.
Email: dr_arumkrismi@staff.ukdw.ac.id

Abstract

Chronic kidney disease-associated pruritus (CKD-aP) is a common and distressing symptom for patients with CKD and a difficult challenge for nephrologists and dermatologists. Recent results showed the multifactorial nature of the pathophysiology, and therapeutic trials were only successful in certain subsets of patients. The clinical manifestations are varied, with xerosis being the most common dermatological manifestation and correlated with the intensity of CKD-aP. A better understanding of the pathophysiology of xerosis in CKD-aP and appropriate topical treatment could correct xerosis to reduce the intensity of CKD-aP and improve the patient's quality of life.

KEYWORDS

chronic kidney disease, moisturizers, pruritus, topical treatment, xerosis

INTRODUCTION

Chronic kidney disease-associated pruritus (CKD-aP) is a common and distressing symptom for patients with CKD and a difficult challenge for nephrologists and dermatologists.[1,2] Kidney Disease: Improving Global Outcome (KDIGO) in 2013 recommended pruritus as one of the criteria to start renal replacement therapy (RRT) in patients with CKD.[3] One of the most common clinical manifestations in patients with CKD-aP is dry skin or xerosis.[4–7] Added to the fact that trials of both systemic and topical therapy were only successful in certain subsets of patients, the multifactorial pathophysiology, poor medical and psychological outcomes in patients with CKD-aP, with the absence of standardized guidelines for diagnosis criteria and therapy have caused CKD-aP to be one of the main research priorities in patients with CKD.[2,8] This narrative review aimed to discuss the epidemiology and disease outcomes of CKD-aP in hemodialysis (HD) patients, pathophysiology of CKD-aP, pathophysiology of xerosis in CKD-aP, diagnostic criteria, and therapy with a focus on topical therapy to correct xerosis. The main objective of this narrative review was to provide an understanding of the importance of correcting xerosis using appropriate topical therapy.

EPIDEMIOLOGY AND DISEASE OUTCOME

Pruritus can occur in all CKD criteria, both in patients who have not or have undergone dialysis. The prevalence of CKD-aP who have not undergone dialysis varies between 16.3% and 64% and does not correlate with CKD

criteria.[5,9] Hu et al.[10] conducted a meta-analysis of 46 cross-sectional studies on the prevalence of CKD-aP in adults who had undergone RRT. The overall prevalence for CKD-aP undergoing dialysis was 55%, 55% in HD patients, and 56% in peritoneal dialysis (PD) patients.

Rayner et al.[11] reported a decline in the overall prevalence of CKD-aP in HD patients from countries enrolled in the Dialysis Outcomes and Practice Patterns Study (DOPPS) from 28% in 1996 to 18% in 2015. Nonetheless, this prevalence varies widely between participating countries from 26% in Germany to 48% in the United Kingdom. Similar results could be found in Indonesia. The 11th Indonesian Renal Registry (IRR) in 2018 reported only 10,807 (8%) patients with complaints of pruritus as an intradialytic complication from a total of 132,142 active HD patients.[12] However, Wiraputranto et al.[13] reported a 40% prevalence of CKD-aP undergoing HD in a hospital in Jakarta, Indonesia.

CKD-aP occurs more frequently in patients who have been on dialysis for ≥3 months and ≤10 years,[14,15] and it was found to be more common in males (although some studies have shown a higher prevalence in females).[15–17] Hemodialyzed patients with CKD-aP were slightly older,[9,11] but other studies reported younger age.[7,13]

CKD-aP is a significant predictor for 24-month cardiovascular mortality in HD patients.[18] Patients with CKD-aP also had higher infection-related hospitalization, major adverse cardiac and cerebrovascular events, catheter-related infection, heart failure, and parathyroidectomy.[19] Rates of cardiovascular and infection-related deaths and hospitalizations were higher for patients with more intense CKD-aP.[9]

CKD-aP correlates with sleep quality, quality of life, depression, and mortality. Patients with moderate to severe CKD-aP had significantly worse sleep quality than those without pruritus.[20,21] This poor sleep quality affects their quality of life,[14] which was significantly associated with the patient's level of depression.[22] Poorer sleep quality increased the mortality rate in patients with CKD-aP.[14] Patients with severe CKD-aP were also less compliant with HD treatment.[9,21]

PATHOPHYSIOLOGY

Pathophysiology of CKD-aP

Pruritus, or itch, is defined as an unpleasant sensation that causes the urge to scratch. The sensation of pruritus is caused by the binding of pruritogens to their receptors (pruriceptors) found in peripheral sensory afferent nerve fibers, namely C and Aδ nerve fibers.[23,24] Pruritogens could derived from outside (exogenous) and inside the body (endogenous). Pro-inflammatory mediators are an example of an endogenous pruritogen.[25,26]

Based on the duration and innervation pathway, pruritus is divided into acute, which is transmitted via the histaminergic pathway, and chronic (lasts ≥6 weeks), which is transmitted via the nonhistaminergic pathway.[24,27] All mediators other than histamine that could trigger pruritus either by binding to pruriceptors or directly activating transient receptor potential vanilloid 1 (TRPV1) and/or transient receptor potential ankyrin 1 (TRPA1), are mediators of chronic pruritus.[23,24] Chronic pruritus is associated with many systemic diseases, one of which is CKD-aP.[27]

Verduzco and Shirazian grouped the pathophysiologic mechanism of CKD-aP based on the results of cross-sectional and case–control studies that have been conducted, into four theories: toxin deposition, peripheral neuropathy, immune system dysregulation, and opioid imbalance.[28] Nevertheless, therapeutic research based on the above-mentioned pathophysiological theories, whether given systemically or topically, has not yet been able to completely cure CKD-aP.[8]

The earliest toxin deposition theory proposed that the deposition of urea in the skin and subcutaneous tissue causes pruritus. This concept is what underlies the use of the term "uremic pruritus."[28] Pruritus is one of the signs and symptoms of the uremic syndrome caused by the biologic effects of toxins that cannot be excreted by the kidneys, but the retention of toxins is a complex problem involving many more solutes than urea and creatinine.[29,30] This toxin deposition theory is supported by the reduced prevalence of CKD-aP along with improvements in HD technique.[11]

The peripheral neuropathy theory was based on the research by Johansson et al.,[31] as well as research by Zakrzewska-Pniewska and Jędras.[32] Johansson et al. showed that HD patients had abnormal skin innervation patterns.[31] Examination of the somatic and autonomic nervous systems performed by Zakrzewska-Pniewska and Jędras in HD patients concluded that peripheral somatic neuropathy was correlated more strongly with the onset of pruritus in this group of patients.[32] The results of the two studies above are supported by research by Gunal et al. [33] which showed that gabapentin was effective in reducing the pruritus intensity of HD patients with CKD-aP.

The immune system dysregulation theory was based on the increase in inflammatory markers, both cutaneous and systemically, in HD patients with CKD-aP. These markers of inflammation include T-helper 1 cells, C-reactive protein, ferritin, and pro-inflammatory cytokines (interleukin [IL]-2, IL-31).[14,34–37] Inflammation that occurs systemically increased the levels of pro-inflammatory

cytokines in the blood, which then bind to their respective receptors on C nerve fibers and trigger the pruritus.[24]

Opioids can trigger or reduce pruritus depending on their binding to certain receptors. Opioids binding to μ-receptors will trigger pruritus, whereas opioids binding to κ-receptors will reduce pruritus.[23,38] This opioid imbalance theory is supported by the effectiveness of κ-receptor agonist therapy in reducing the pruritus intensity of HD patients with CKD-aP.[39,40]

Pathophysiology of xerosis on CKD-aP

HD patients with CKD-aP had significantly lower stratum corneum (SC) hydration than those without pruritus.[41] Yosipovitch et al.[42] showed that impaired integrity of SC is the result of a decrease in glycerol content which is significantly correlated with xerosis in HD patients. Research by Chorazyczewska et al.[43] showed that there was a change in the lipid composition of SC in HD patients. This change in the lipid composition of SC causes an increase in transepidermal water loss (TEWL) and provides a clinical picture of xerosis in HD patients.

The most dominant function of the epidermal barrier as a permeability barrier that regulates TEWL and hydration of the epidermis, is mainly played by SC.[44] The SC performs its function as a permeability barrier through two main components: the protein-rich matrix in the form of corneocytes, and the intercellular lipid-rich matrix.[45] The intercellular lipid-rich matrix in SC consists of ceramide, cholesterol, and free fatty acids (FFAs) with an equimolar ratio of 1:1:1 and is essential for regulating TEWL and maintaining SC hydration.[46]

Loss of intercellular lipids will cause disturbances in the balance of water content in SC due to increased TEWL and decreased SC hydration. Disruption of the water content in the SC will interfere with the function of the protease enzyme so that corneocytes desquamate in clusters and manifest as dry skin or xerosis. Dry skin looks dull, rough, not supple, scaly, also appearing peeling, sometimes with erythematous patches and even fissures, and can be accompanied by pruritus.[44,47,48] Protease enzymes involved in corneocyte desquamation can also activate protease-activated receptors involved in the pathophysiology of chronic pruritus.[26]

DIAGNOSIS AND CLINICAL MANIFESTATIONS

To date, there are no standardized guidelines to diagnose CKD-aP. Generally, CKD-aP was defined as persistent pruritus for ≥6 weeks without any form of primary skin lesion,[4,49] which was directly related to kidney disease without any other possible systemic or dermatologic conditions that can cause pruritus.[28] Pruritus is generally felt every day or almost every day, more severe at night,[20] and can appear either before, during, or after dialysis session.[28,50] Pruritus may be aggravated by rest, heat, sweat, and stress; and relieved by physical activities, cold temperatures, and bathing with either hot or cold water.[50,51] As much as 50% of pruritus is distributed with bilateral symmetry over large areas of the body, but can also be localized to the back (most often), head, face, arms, and abdomen.[20,50]

Dermatological manifestations vary widely from no lesion at all, xerosis, to excoriations and other secondary lesions due to scratching such as erosion, ulceration, crusting, with or without secondary bacterial infection.[52] One of the dermatological manifestations that were significantly different in patients with CKD-aP is dry skin or xerosis.[4–7] Xerosis was found in 45.1%–67.1% of CKD-aP patients undergoing HD[4,6] and correlated with the intensity of CKD-aP.[5,6,53]

Assessment of the intensity of pruritus is a major problem in evaluating the severity and outcome of therapy in CKD-aP.[54] Four methods that commonly used to assess the intensity of pruritus were the Visual Analog Scale (VAS), Numerical Rating Scale (NRS), Verbal Rating Scale (VRS), and a question from the Kidney Disease Quality of Life-Short Form (KDQOL-SF).[28] The European Network on Assessment of Severity and Burden of Pruritus (PruNet) concluded that 24-h Worst Itching Intensity (WI)-VAS/NRS/VRS and 24-h average itching intensity VAS/NRS/VRS were valid instruments with good reproducibility and internal consistency in the countries involved.[55] While WI-VAS was the best reproducible and consistent measuring instrument,[55] WI-NRS was used in a global clinical trial to assess the efficacy of difelikefalin in subjects with CKD-aP.[40,56–58] Beside those three validated methods, a question from the KDQOL-SF can also be used to measure the intensity of pruritus, as has been done by the DOPPS.[9,11,14,59]

VAS is the most frequently used method for subjective assessment of the intensity of pruritus.[60] A meta-analysis conducted by Hu et al.[10] showed that VAS was used in 26 of the 46 cross-sectional studies analyzed, while 20 studies used several other methods such as KDQOL-SF, Dialysis Symptom Index, and interview. The VAS assessment of pruritus was performed using a 10 cm horizontal line with a 0 (zero) point on the left and a 10 (ten) point on the right. Zero point indicates no pruritus, and 10 point indicates "worst imaginable itch." Patients were asked to give a mark or draw a vertical line on the horizontal line according to their subjective intensity of pruritus.[54] Reich et al.[61] recommend the cutoff

TABLE 1 Studies of topical treatments for CKD-aP.

Reference, year Trial design	Trial populations Sample size Gender Mean age [age range] in years	Treatments	Concurrent medications	Outcome measures	Results
Tarng et al.[67]	HD	Capsaicin cream 0.025% applied four times daily for 4 weeks or Placebo cream	Discontinued all topical treatments other than moisturizers 2 weeks before trial. Continued other ongoing medications	At baseline and weekly intervals: 1. self-assessment of itching 2. investigators assessment of skin dryness and erythema	Capsaicin cream 0.025% was significantly more effective in improving the itching score with prolonged antipruritic effect
Crossover RCT 2 w washout	17 12m, 5f 62.9 ± 15.6 [27–85]	Followed with no treatment for 8 weeks			
Okada and Matsumoto[68]	HD	Aqueous gel containing 80% water applied twice daily for 2 weeks followed with no treatment for 2 weeks or Not treated with any emollient for 4 weeks	Discontinued all emollient such as antihistamine and urea-containing ointment. Continued other ongoing medications	At baseline and every 2 weeks: 1. self-assessment on VAS 2. clinical assessments by two doctors (blinded) for skin dryness and scratching	Aqueous gel containing 80% water significantly decreased VAS, skin dryness, and scratching compared with that at baseline ($p < 0.01$)
Not stated	20 8m, 12f 67.2 ± 9.8				
Duque et al.[69]	HD	Tacrolimus ointment 0.1% applied twice daily by the patients and three times weekly by investigators for 4 weeks or Placebo	Discontinued all topical and systemic medications including corticosteroids 2 weeks and antihistamines 4 weeks before trial. Prohibited any other topical medications or moisturizers during 6 weeks trial periods	At baseline, Weeks 4 and 6: 1. self-assessment on VAS 2. clinical evaluation by investigators (excoriations, scaliness, lichenification, and overall severity)	Tacrolimus ointment 0.1% was not more effective than placebo
RCT	20 Gender not reported 59 ± 13.2	Followed with no treatment for 2 weeks			
Szepietowski et al.[70]	HD	Cream with structured natural lipids containing endocannabinoids (AEA and PEA) applied twice daily for 3 weeks	Discontinued all antipruritic treatments 4 weeks before trial	At baseline, weekly intervals, and 2 weeks of discontinuation: 1. self-assessment on VAS 2. investigators assessment of pruritus score and dry skin score	Cream with structured natural lipids containing endocannabinoids significantly decreased VAS, pruritus score, and dry skin score during application period ($p < 0.0001$)
Not stated	21 11m, 10f 58 [31–81]	Followed with no treatment for 2 weeks			

(Continues)

TABLE 1 (Continued)

Reference, year Trial design	Trial populations Sample size Gender Mean age [age range] in years	Treatments	Concurrent medications	Outcome measures	Results
Chen et al.[71] Crossover RCT 2 w washout	HD and PD 16	GLA cream 2.2% applied once daily to entire body and three times daily to pruritic sites for 2 weeks or Placebo cream	Discontinued all antipruritic treatments 2 weeks before trial	Before and after treatment periods: 1. self-assessment on VAS 2. self-assessment on pruritus score	GLA cream 2.2% had greater antipruritic effect during application period on both groups, with prolonged antipruritic effect
Boaz et al.[72] RCT	HD 65 37m, 28f 67.8 ± 12.9	Body lotion enriched with minerals from DS applied twice daily or P1: lotion with no DS minerals but otherwise identical to DS or P2: lotion with no active ingredients	Discontinued all antipruritic treatments 2 weeks before trial. Continued other ongoing medications	At baseline and week 2: self-assessment of itching, dryness, peeling, and tightness	DS was not superior to either of the placebo treatments in the symptomatic relief of CKD-aP
Young et al.[73] RCT	HD 28 m to f ratio = 1:1 Not reported [21–70]	Pramoxine HCl lotion 1% applied twice daily for 4 weeks or Placebo lotion (bland emollient)	Discontinued all antipruritic treatments	1. Every day: self-assessment on VAS 2. At baseline, Weeks 1 and 4: erythema, xerosis, and lichenification 3. At baseline and Week 4: skin hydration measurement using the MoistureMeter piko™ (Delfin Technologies Ltd)	Pramoxine HCl lotion 1% significantly decreased VAS ($p < 0.01$) No significant differences were displayed in other studied disease-related variables
Makhlough[74] Crossover RCT 2 w washout	HD 34 14m, 20f 57.0 ± 18.6	Capsaicin ointment 0.03% rubbed four times daily for 4 weeks or Placebo	Not recorded	At baseline and weekly intervals: investigators assessment on pruritus score	Capsaicin ointment 0.03% significantly decreased pruritus score ($p < 0.001$)
Balaskas et al.[75]	HD or PD	Emulsion combining glycerol and paraffin (test product) applied twice daily for	Excluded: treated with any moisturizing or emollient preparations within 7 days, modified dosage of	1. At baseline and Day 7: scaling using D-Squame® technique	Test product was significantly effective on treatment response and objective reduction in

(Continues)

TABLE 1 (Continued)

Reference, year Trial design	Trial populations Sample size Gender Mean age [age range] in years	Treatments	Concurrent medications	Outcome measures	Results
		7 days or Emulsion alone (comparator) Followed by open labeled use of test product for 49 days for both groups	antipruritics within 4 weeks, phototherapy within 8 weeks before trial	2. At Day 7: xerosis using modified El Gammal clinical score & 3-point categorical scale 3. At baseline and Day 56: self-assessment on SF-12 and DLQI 4. At baseline, Days 28 and 56: self-assessment on VAS	the density and thickness of the scales ($p < 0.0001$)
RCT to open-label trial	99 53m, 46f 63.16 ± 1.28 [18–89]				
Castello and Milani[76] Open-label trial	HD 15 3m, 12f 66 [40–84]	10% urea ISDIN® plus dexpanthenol lotion applied twice daily for 4 weeks	Discontinued all topical treatments	At baseline and every 2 weeks: 1. IS 2. SRRC	10% urea ISDIN® plus dexpanthenol lotion significantly decreased IS and SRRC ($p< 0.01$)
Lin et al.[77] Pretest—post-test quasi-experimental	HD 93 55m, 38f 61.88 ± 12.7	Chilled baby oil (intervention group 1) for 15 min at least once daily for 3 weeks or Un-chilled baby oil (intervention group 2) or No intervention	Not recorded	At baseline and Week 3: self-assessment on ISS	Chilled and un-chilled baby oil significantly improved pruritus compared with the control group, but did not differ between intervention groups 1 and 2
Aramwit et al.[78] RCT	HD 47 17m, 30f 49.6 ± 11.2	Sericin cream for 6 weeks or Placebo cream	Not recorded	At baseline and every 2 weeks: 1. self-assessment on VAS 2. Skin Diagnostic SD27 (skin hydration, irritation, and pigmentation) At baseline and week 6: self-assessment on KDQOL-SF	Sericin cream significantly improved skin hydration, irritation, and pigmentation compared with placebo ($p < 0.01$)
Feily et al.[79] RCT	HD 60 38m, 22f	Cromolyn sodium cream 4% twice daily for 4 weeks or Placebo	Discontinued all antipruritic treatments 2 weeks before trial. Continued other ongoing medications	At baseline and weekly intervals: self-assessment on VAS (0–5)	Cromolyn sodium cream 4% was significantly reducing pruritus in the

(Continues)

TABLE 1 (Continued)

Reference, year Trial design	Trial populations Sample size Gender Mean age [age range] in years	Treatments	Concurrent medications	Outcome measures	Results
	53 ± 11.4				third and fourth week ($p < 0.05$)
Jung et al.[80] Open-label trial	HD 20 6m, 14f Not reported [50–77]	Vitamin D (calcipotriol) solution twice daily for 4 weeks or Placebo solution	Continued all antipruritic treatments	At baseline and every 2 weeks: 1. self-assessment on VMPAS 2. self-assessment on VAS 3. clinical and dermoscopic photographs	Vitamin D (calcipotriol) solution significantly improved dry dermoscopic findings, decreased VMPAS and VAS compared with the placebo ($p < 0.05$)
Nakhaee et al.[81] Crossover RCT 3 d washout	HD 23 17m, 6f 57.04 ± 12.20	*Avena sativa* lotion twice daily for 2 weeks or Topical diluted vinegar or Hydroxyzine tablets	Discontinued antipruritic treatment 24 h before trial	Before and after each intervention period: self-assessment on VAS	All of the three treatments significantly decreased the mean scores of pruritus intensity ($p < 0.001$)
Imani et al.[82]	HD	*Sambucus ebulus* gel 2% twice daily for 8 weeks or Placebo gel	Continued all antipruritic treatments	At baseline, Weeks 4 and 8: 1. self-assessment on pruritus severity scale (1–48) 2. xerosis in pruritus area	*Sambucus ebulus* gel 2% significantly decreased the pruritus severity scores at fourth and eighth week compared with baseline
RCT	61				No significant difference in pruritus severity scale between two groups at fourth and eighth week
	31m, 30f				No significant reduction of xerosis in two groups
	55.9 ± 11.7 (intervention) versus 59.97 ± 13.88 (control)				
Mehri et al.[83] RCT	HD 42	Sweet almond oil once daily for 2 weeks or Routine care	Not recorded	At baseline and weekly intervals: itchyQoL instrument	Sweet almond oil significantly improved itchyQoL ($p < 0.05$)

(Continues)

TABLE 1 (Continued)

Reference, year Trial design	Trial populations Sample size Gender Mean age [age range] in years	Treatments	Concurrent medications	Outcome measures	Results
	22m, 20f 57 ± 17.1 (intervention) versus 50.7 ± 16.4 (control)				
Yahya et al.[84] RCT	HD 65 34m, 31f Not reported [<30 to >71]	Urea 20% in the cream base of NaPCA and vegetable oil twice daily for 4 weeks or Placebo in the cream base of NaPCA	Excluded: treated with systemic corticosteroid, antihistamines, herbal remedies, vitamins, supplements 4 weeks before trial; topical skin moisturizers, emollients, corticosteroids, retinoids, and antipruritics 2 weeks before trial	At baseline and every 2 weeks: 1. self-assessment on VAS 2. skin hydration using Corneometer (SM815; Courage + Khazaka Electronic GmbH)	Urea 20% in the cream base of NaPCA significantly decreased VAS and increased corneometer
Khorsand et al.[85] RCT	HD 52 31m, 21f 51.88 ± 14.98 (intervention) versus 51.59 ± 14.59 (control)	Massage with violet oil for 7 min during six sessions (2 weeks) or Without violet oil	Discontinued all antipruritic treatments 2 weeks before trial. Continued other ongoing medications	After each session: 1. self-assessment on VAS 2. skin dryness questionnaire	Massage with violet oil significantly reduced VAS and skin dryness score
Aquino et al.[86] RCT	HD 30 26m, 4f 46.1 ± 13.4 [29–70] (intervention) versus 41.2 ± 11.6 [27–62] (control)	Gabapentin cream 6% applied once daily for 2 weeks or Plain permeation cream	Excluded: treated with all antipruritic medications 1 week before trial. Discontinued all topical medications	At baseline, Weeks 1 and 2: self-assessment on VAS	Gabapentin cream 6% significantly decreased mean pruritus scores compared with baseline ($p < 0.001$)

(Continues)

TABLE 1 (Continued)

Reference, year Trial design	Trial populations Sample size Gender Mean age [age range] in years	Treatments	Concurrent medications	Outcome measures	Results
Yoshida et al.[87] Open-label RCT	HD 71 48m, 23f 62.9 ± 11.4 [20–80]	Heparinoid-containing lotion twice daily for 2 or 8 weeks	Discontinued any other heparinoid-containing products, urea preparations, or petrolatum. Continued other ongoing medications	At baseline, Weeks 1, 2, 3, 4, 6, and 8: 1. Primary endpoint at week 4: WCSC (Corneometer and Multi Display Devices MDD4; Courage + Khazaka Electronic GmbH) 2. Secondary endpoint: a. skin dryness score b. self-assessment on VAS and DLQI	Significant improvement of all endpoints in both group during the trial period ($p < 0.05$)

Abbreviations: AEA, N-acetylethanolamine; DLQI, Dermatology Life Quality Index, DS, Dead Sea; GLA, gamma-linolenic acid; HCl, hydrochloride; HD, hemodialysis; IS, itching score; ISS, itch severity scale; KDQOL-SF, Kidney Disease Quality of Life-Short Form; NaPCA, sodium pidolat sodium lactate; P1/P2, placebo 1/ 2, PD, peritoneal dialysis; PEA, N-palmitoylethanolamine; QoL, quality of life; SF-12, generic scale short form-12 questionnaire; SRRC, scaling, roughness, redness, and cracks fissures; VAS, visual analog scale; VMPAS, validated modified pruritus assessment score; WCSC, water content of the stratum corneum.

values for VAS as no pruritus (score 0), mild pruritus (scores 1–3), moderate (4–6), severe (7–8), and very severe (9–10).

In addition to intensity, assessment of pruritus using VAS and KDQOL-SF can also be used to determine whether the patient has pruritus or not. Momose et al.[62] stated that patients with pruritus were those with moderate to very severe pruritus category. Patients with mild pruritus should be excluded from a treatment trial because of the tendency for the intensity of pruritus to vary depending on the day and time.

TREATMENT

Treatment of pruritus should be based on the underlying pathophysiology. However, it is difficult to apply this to CKD-aP given the insufficient evidence to provide concrete recommendations regarding the treatment of CKD-aP.[63] Pruritus that is localized or of mild intensity can be treated using topical treatment, but generalized or severe pruritus requires systemic treatment. European S2k guidelines for chronic pruritus suggest the daily use of moisturizers, especially after bathing to improve skin barrier and reduce the intensity of pruritus.[64] Decreasing serum phosphorus levels, increasing dialysis adequacy, the use of systemic drugs such as antihistamines, gabapentin, and nalfurafine, as well as various kinds of topical treatments have been widely used for CKD-aP, but these actions have not been able to completely cure CKD-aP.[8]

Topical treatment

Topical treatment is the mainstay therapy for pruritus caused by disruption of the epidermal barrier. Topical treatment can provide immediate improvement in affected skin areas with minimal risk of systemic effects.[26,65] Combs et al.[66] stated that improving SC hydration was the cornerstone of CKD-aP treatment. Topical treatment can improve the integrity of the SC barrier, thereby correcting xerosis and reducing the pruritus intensity.[8,66] Various topical treatments have been used in the management of CKD-aP with varying results (Table 1).

Research on topical treatment for CKD-aP has been started since 1996 with various study designs, sample sizes, topical forms, concurrent medications, and outcome measures. However, almost all active ingredients used as topical treatment in these studies were shown to significantly reduce pruritus intensity, except Tacrolimus ointment 0.1%[69] and Dead Sea (DS) minerals.[72] In studies that measure skin dryness/skin hydration as one of the outcomes, these various topical forms (gels, creams, emulsions, lotions, and solutions) can also reduce skin dryness or improve skin hydration.[68,70,75,76,78,80,84,85,87]

Topical drug preparations consist of active ingredients (drugs) in a base (vehicle), and excipients (e.g., emulsifiers, antioxidants, and preservatives).[65,88] A good topical drug preparation contains a composition of basic ingredients that can improve the function of the epidermal barrier.[44]

Topical drugs were classified based on their form into monophase, two-phase, and three-phase. Monophase is a pure form consisting of three basic forms: solid, liquid, and oil. Two-phase is a combination of two basic forms. Combination of liquid and oil forms will produce creams (water-in-oil emulsion) and lotions (oil-in-water emulsion).[65,89] Lotion contains a liquid phase of more than 31%, so it can be applied easily, easy to clean with water, and less oily so that it is more comfortable for daily use.[44,89] Creams and lotions are the two most commonly used formulation of moisturizers.[90] Immediately after being applied the water phase will evaporate, leaving an oil phase (lipid) and active ingredients on the surface of the skin.[89]

Moisturizer is an important component in the management of xerosis. The use of moisturizers can replace the loss of intercellular lipids and repair corneocytes, thereby preventing TEWL and maintaining SC hydration.[91] The return of SC hydration to normal levels will reduce cytokine production.[92]

Properly designed moisturizers should contain a combination of occlusive, humectants, emollients, and other active ingredients such as ceramides, vitamins, and herbal extracts.[44,88] Occlusive ingredients (e.g., petrolatum, squalene, fatty acids, and cholesterol) will coat the skin's surface with a water-repellent lipid layer that blocks the entry and exit of water. Humectants (e.g., glycerin and urea) will absorb water from the surrounding environment, while emollients (e.g., dimethicone and cyclomethicone) will provide a smooth and soft texture on the skin's surface.[44,92] The combination of various occlusive, humectant, and emollient ingredients with different percentages produces different moisturizing formulations. However, all moisturizing preparations still have about 80% of the same components.[93]

Specially formulated moisturizers contain lipids with a composition and ratio similar to intercellular lipids (ceramide:cholesterol:FFA in a ratio of 1:1:1) can improve skin barrier function more quickly.[94] The composition and ratio similar to that of intercellular lipids will be absorbed more quickly by SC until it reaches the stratum granulosum (SG), and combines with intercellular lipids produced by lamellar bodies in SG.[94,95]

Moisturizers should be used 1–3 times a day immediately after bathing to obtain the optimal occlusive effect of hydrated SC from bathing.[92] The fingertip unit (FTU) is a practical guide that can be used to calculate the

amount of ointment (monophase form of oil) needed in one application. One FTU (equivalent to 0.5 g) is the amount of ointment dispensed from the tip of a 5 mm diameter tube from the distal fold to the tip of an adult index finger, which can be applied to an area the size of two adult palms.[65]

The use of moisturizers rarely causes serious adverse effects, even when used on large areas of the body for long periods of time. However, adverse effects may occur with the use of any topical preparations. Most frequent adverse effects of using moisturizers were usually sensory reactions or subjective sensations immediately after application, with or without signs of inflammation. The most common symptoms include sensation of discomfort, burning/hot sensation, stinging, pruritus, and/or pain, especially in the face and skin folds.[90,96] To date, there are no contraindications to the use of moisturizers. However, care should be taken in choosing moisturizer for patients with a history of atopic dermatitis.[92,96]

Experience from the field

Less than 50% of patients with CKD-aP reported their symptom to a nephrologist, followed by reporting it to a nurse or other dialysis staff member (32%), or a primary care doctor (16.5%). Only 18% of patients with CKD-aP reported their symptom to a dermatologist, and 17% patients had not reported their symptoms to any health care provider. About 69% of medical directors underestimated the prevalence of pruritus in their facilities.[11] The lack of reporting the symptoms by the patients and the underestimation by the medical directors might be due to lack of knowledge on causes and treatment, lack of proper attitudes toward the importance of pruritus as a health issue, and lack of prompts for pruritus assessment during consultation.[97]

CONCLUSIONS

Pruritus is a common and distressing symptom in patients with CKD, with various adverse clinical and psychological outcomes. Xerosis was commonly found in patients with CKD-aP, and correlated with the intensity of CKD-aP. Appropriate topical treatment to correct xerosis may help reduce the intensity of CKD-aP and improve patient's quality of life.

ACKNOWLEDGMENTS

The authors acknowledge the staff of Klinik Bahasa Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ORCID

Arum Krismi https://orcid.org/0000-0003-4276-3025

REFERENCES

1. Germain MJ. Uremic pruritus: an itch with ominous consequences. Am J Nephrol. 2017;46(6):448–9.
2. Weisshaar E, Ofenloch RF. One step closer to alleviating uraemic pruritus. Nat Rev Nephrol. 2020;16(4):189–90.
3. KDIGO. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease: referral to specialists and models of care. Kidney Int Suppl. 2013;3:112–9.
4. Weiss M, Mettang T, Tschulena U, Passlick-Deetjen J, Weisshaar E. Prevalence of chronic itch and associated factors in haemodialysis patients: a representative cross-sectional study. Acta Derm Venereol. 2015;95(7):816–21.
5. Solak B, Acikgoz SB, Sipahi S, Erdem T. Epidemiology and determinants of pruritus in pre-dialysis chronic kidney disease patients. Int Urol Nephrol. 2016;48(4):585–91.
6. Ozen N, Cinar FI, Askin D, Mut D. Uremic pruritus and associated factors in hemodialysis patients: a multi-center study. Kidney Res Clin Pract. 2018;37(2):138–47.
7. Hu T, Wang B, Liao X, Wang S. Clinical features and risk factors of pruritus in patients with chronic renal failure. Exp Ther Med. 2019;18:964–71.
8. Martin CE, Clotet-Freixas S, Farragher JF, Hundemer GL. Have we just scratched the surface? A narrative review of uremic pruritus in 2020. Can J Kidney Heal Dis. 2020;7:1–14.
9. Sukul N, Karaboyas A, Csomor PA, Schaufler T, Wen W, Menzaghi F, et al. Self-reported pruritus and clinical, dialysis-related, and patient-reported outcomes in hemodialysis patients. Kidney Med. 2021;3(1):42–53.
10. Hu X, Sang Y, Yang M, Chen X, Tang W. Prevalence of chronic kidney disease-associated pruritus among adult dialysis patients a meta-analysis of cross-sectional studies. Medicine. 2018;97(21):1–7.
11. Rayner HC, Larkina M, Wang M, Graham-Brown M, van der Veer SN, Ecder T, et al. International comparisons of prevalence, awareness, and treatment of pruritus in people on hemodialysis. Clin J Am Soc Nephrol. 2017;12(12):2000–7.
12. PERNEFRI. 11th Report of Indonesian Renal Registry 2018. Indones ren Regist 2018;1–46.
13. Wiraputranto MC, Agustinus OP, Kuntjoro T, Syamsuddin H. Uremic pruritus characteristics in hemodialysis patients with chronic kidney disease in relation to blood urea levels and dialysis adequacy at Jakarta Pelabuhan Hospital, Indonesia. Proc 23rd Reg Conf Dermatol 2018;68–72.
14. Pisoni RL, Wikström B, Elder SJ, Akizawa T, Asano Y, Keen ML, et al. Pruritus in haemodialysis patients: international results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrol Dial Transplant. 2006;21(12):3495–505.
15. Kfoury LW, Jurdi MA. Uremic pruritus. J Nephrol. 2012;25(5):644–52.

16. Robles-Mendez JC, Vazquez-Martinez O, Ocampo-Candiani J. Skin manifestations of chronic kidney disease. Actas Dermo-Sifiliogr (Engl Ed). 2015;106(8):609–22.
17. Ko CJ, Cowper SE. Dermatologic conditions in kidney disease. In: Yu ASL, Chertow GM, Luyckx VA, Marsden PA, Skorecki K, Taal MW, editors. Brenner and Rector's the kidney. 11th ed. Philadelpia: Elsevier Inc.; 2020. p. 1932–44.
18. Weng CH, Hu CC, Yen TH, Hsu CW, Huang WH. Uremic pruritus is associated with two-year cardiovascular mortality in long term hemodialysis patients. Kidney Blood Press Res. 2018;43(3):1000–9.
19. Ting SW, Fan PC, Lin YS, Lin MS, Lee CC, Kuo G, et al. Uremic pruritus and long-term morbidities in the dialysis population. PLoS One. 2020;15(10):1–15.
20. Mathur VS, Lindberg J, Germain M, Block G, Tumlin J, Smith M, et al. A longitudinal study of uremic pruritus in hemodialysis patients. Clin J Am Soc Nephrol. 2010;5(8): 1410–9.
21. Ramakrishnan K, Bond TC, Claxton A, Sood VC, Kootsikas M, Agnese W, et al. Clinical characteristics and outcomes of end-stage renal disease patients with self-reported pruritus symptoms. Int J Nephrol Renovasc Dis. 2013;7:1–12.
22. Suseł J, Batycka-Baran A, Reich A, Szepietowski JC. Uraemic pruritus markedly affects the quality of life and depressive symptoms in haemodialysis patients with end-stage renal disease. Acta Derm Venereol. 2014;94(3):276–81.
23. Chuquilin M, Alghalith Y, Fernandez KH. Neurocutaneous disease: cutaneous neuroanatomy and mechanisms of itch and pain. J Am Acad Dermatol. 2016;74(2):197–212.
24. Yosipovitch G, Rosen JD, Hashimoto T. Itch: from mechanism to (novel) therapeutic approaches. J Allergy Clin Immunol. 2018;142(5):1375–90.
25. Storan ER, O'Gorman SM, McDonald ID, Steinhoff M. Role of cytokines and chemokines in itch. Handb Exp Pharmacol. 2015;226:163–76.
26. Yosipovitch G, Misery L, Proksch E, Metz M, Ständer S, Schmelz M. Skin barrier damage and itch: review of mechanisms, topical management and future directions. Acta Derm Venereol. 2019;99(13):1201–9.
27. Ständer S, Weisshaar E, Mettang T, Szepietowski JC, Carstens E, Ikoma A, et al. Clinical classification of itch: a position paper of the international forum for the study of itch. Acta Derm Venereol. 2007;87(4):291–4.
28. Verduzco HA, Shirazian S. CKD-associated pruritus: new insights into diagnosis, pathogenesis, and management. Kidney Int Rep. 2020;5(9):1387–402.
29. Dobre MA, Meyer TW, Hostetter TH. The uremic syndrome. In: Kimmel PL, Rosenberg MA, editors. Chronic renal disease. Amsterdam: Elsevier Inc. 2015. p. 83–91.
30. Vanholder R, Fouque D, Glorieux G, Heine GH, Kanbay M, Mallamaci F, et al. Clinical management of the uraemic syndrome in chronic kidney disease. Lancet Diabetes Endocrinol. 2016;4(4):360–73.
31. Johansson O, Hilliges M, Ståhle-Bäckdahl M. Intraepidermal neuron-specific enolase (NSE)-immunoreactive nerve fibres: evidence for sprouting in uremic patients on maintenance hemodialysis. Neurosci Lett. 1989;99(3):281–6.
32. Zakrzewska-Pniewska B, Jędras M. Is pruritus in chronic uremic patients related to peripheral somatic and autonomic neuropathy? Neurophysiol Clin Neurophysiol. 2001;31(3):181–93.
33. Gunal AI, Ozalp G, Yoldas TK, Gunal SY, Kirciman E, Celiker H. Gabapentin therapy for pruritus in haemodialysis patients: a randomized, placebo-controlled, double-blind trial. Nephrol Dial Transplant. 2004;19(12):3137–9.
34. Kimmel M, Alscher DM, Dunst R, Braun N, Machleidt C, Kiefer T, et al. The role of micro-inflammation in the pathogenesis of uraemic pruritus in haemodialysis patients. Nephrol Dial Transplant. 2006;21(3):749–55.
35. Fallahzadeh MK, Roozbeh J, Geramizadeh B, Namazi MR. Interleukin-2 serum levels are elevated in patients with uremic pruritus: a novel finding with practical implications. Nephrol Dial Transplant. 2011;26(10):3338–44.
36. Ko MJ, Sen PY, Chen HY, Hsu SP, Pai MF, Yang JY, et al. Interleukin-31 is associated with uremic pruritus in patients receiving hemodialysis. J Am Acad Dermatol. 2014;71(6): 1151–1159.e1.
37. Malekmakan L, Malekmakan A, Sayadi M, Pakfetrat M, Sepaskhah M, Roozbeh J. Association of high-sensitive C-reactive protein and dialysis adequacy with uremic pruritus. Saudi J Kidney Dis Transpl. 2015;26(5):890–5.
38. Cowan A, Kehner GB, Inan S. Targeting itch with ligands selective for κ opioid receptors. Handb Exp Pharmacol. 2015; 226:291–314.
39. Kumagai H, Ebata T, Takamori K, Muramatsu T, Nakamoto H, Suzuki H. Effect of a novel kappa-receptor agonist, nalfurafine hydrochloride, on severe itch in 337 haemodialysis patients: a phase III, randomized, double-blind, placebo-controlled study. Nephrol Dial Transplant. 2010;25(4):1251–7.
40. Fishbane S, Mathur V, Germain MJ, Shirazian S, Bhaduri S, Munera C, et al. Randomized controlled trial of difelikefalin for chronic pruritus in hemodialysis patients. Kidney Int Rep. 2020;5(5):600–10.
41. Morton CA, Lafferty M, Hau C, Henderson I, Jones M, Lowe JG. Pruritus and skin hydration during dialysis. Nephrol Dial Transplant. 1996;11(10):2031–6.
42. Yosipovitch G, Duque MI, Patel TS, Ishiuji Y, Guzman-Sanchez DA, Dawn AG, et al. Skin barrier structure and function and their relationship to pruritus in end-stage renal disease. Nephrol Dial Transplant. 2007;22(11):3268–72.
43. Chorążyczewska W, Reich A, Szepietowski JC. Lipid content and barrier function analysis in uraemic pruritus. Acta Derm Venereol. 2016;96(3):402–3.
44. Rosso JQD. Moisturizer and barrier repair formulations. In: Draelos ZD, Dover JS, Alam M, editors. Cosmeceuticals. 3rd ed. Toronto: Elsevier Inc.; 2016. p. 81–9.
45. Kubo A, Amagai M. Skin barrier. In: Kang S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, editors. Fitzpatrick's dermatology. 9th ed. New York: McGraw Hill Education; 2019. p. 207–31.
46. Elias PM. Physiologic lipids for barrier repair. In: Draelos ZD, Dover JS, Alam M, editors. Cosmeceuticals. Third ed. Toronto: Elsevier Inc.; 2016. p. 49–54.
47. Pons-Guiraud A. Dry skin in dermatology: a complex physiopathology. J Eur Acad Dermatol Venereol. 2007;21(Suppl. 2): 1–4.

48. Moniaga CS, Tominaga M, Takamori K. Mechanisms and management of itch in dry skin. Acta Derm Venereol. 2020; 100(1):10–21.
49. Simonsen E, Komenda P, Lerner B, Askin N, Bohm C, Shaw J, et al. Treatment of uremic pruritus: a systematic review. Am J Kidney Dis. 2017;70(5):638–55.
50. Patel TS, Freedman BI, Yosipovitch G. An update on pruritus associated with CKD. Am J Kidney Dis. 2007;50(1):11–20.
51. Zucker I, Yosipovitch G, David M, Gafter U, Boner G. Prevalence and characterization of uremic pruritus in patients undergoing hemodialysis: uremic pruritus is still a major problem for patients with end-stage renal disease. J Am Acad Dermatol. 2003;49(5):842–6.
52. Mettang T, Kremer AE. Uremic pruritus. Kidney Int. 2015; 87(4):685–91.
53. Szepietowski JC, Reich A, Schwartz RA. Uraemic xerosis. Nephrol Dial Transplant. 2004;19(11):2709–12.
54. Furue M, Ebata T, Ikoma A, Takeuchi S, Kataoka Y, Takamori K, et al. Verbalizing extremes of the visual analogue scale for pruritus: a consensus statement. Acta Derm Venereol. 2013;93(2):214–5.
55. Storck M, Sandmann S, Bruland P, Pereira MP, Steinke S, Riepe C, et al. Pruritus Intensity Scales across Europe: a prospective validation study. J Eur Acad Dermatol Venereol. 2021;35(5):1176–85.
56. Fishbane S, Jamal A, Munera C, Wen W, Menzaghi F. A phase 3 trial of difelikefalin in hemodialysis patients with pruritus. N Engl J Med. 2020;382(3):222–32.
57. Wooldridge TD, Mccafferty K, Schoemig M, Csiky BS, Zwiech R, Wen W, et al. Efficacy and safety of difelikefalin for moderate-to-severe CKD-associated pruritus: a global phase 3 study in hemodialysis patients (KALM-2). J Am Soc Nephrol. 2020;31(1):22–3.
58. Topf J, Wooldridge T, McCafferty K, Schömig M, Csiky B, Zwiech R, et al. Efficacy of difelikefalin for the treatment of moderate to severe pruritus in hemodialysis patients: pooled analysis of KALM-1 and KALM-2 phase 3 studies. Kidney Med. 2022;4(8):1–11.
59. Kimata N, Fuller DS, Saito A, Akizawa T, Fukuhara S, Pisoni RL, et al. Pruritus in hemodialysis patients: results from the Japanese dialysis outcomes and practice patterns study (JDOPPS). Hemodial Int. 2014;18(3):657–67.
60. Phan NQ, Blome C, Fritz F, Gerss J, Reich A, Ebata T, et al. Assessment of pruritus intensity: prospective study on validity and reliability of the visual analogue scale, numerical rating scale and verbal rating scale in 471 patients with chronic pruritus. Acta Derm Venereol. 2012;92(5):502–7.
61. Reich A, Chatzigeorkidis E, Zeidler C, Osada N, Furue M, Takamori K, et al. Tailoring the cut-off values of the visual analogue scale and numeric rating scale in itch assessment. Acta Derm Venereol. 2017;97(6):759–60.
62. Momose A, Kudo S, Sato M, Saito H, Nagai K, Katabira Y, et al. Calcium ions are abnormally distributed in the skin of haemodialysis patients with uraemic pruritus. Nephrol Dial Transplant. 2004;19(8):2061–6.
63. Siemens W, Xander C, Meerpohl JJ, Buroh S, Antes G, Schwarzer G, et al. Pharmacological interventions for pruritus in adult palliative care patients. Cochrane Database Syst Rev. 2013;2013(11):CD008320.
64. Weisshaar E, Szepietowski JC, Dalgard F, Garcovich S, Gieler U, Gimenez-arnau A, et al. European S2k guideline on chronic pruritus. Acta Derm Venereol. 2019;99(5):469–506.
65. Fox M, Helfrich Y, Kang S. Other topical medications. In: Bolognia JL, Schaffer JV, Cerroni L, editors. Dermatology. 4th ed. China: Elsevier Ltd; 2018. p. 2153–64.
66. Combs SA, Teixeira JP, Germain MJ. Pruritus in kidney disease. Semin Nephrol. 2015;35(4):383–91.
67. Tarng DC, Cho YL, Liu HN, Huang TP. Hemodialysis-related pruritus: a double-blind, placebo-controlled, crossover study of capsaicin 0.025% cream. Nephron. 1996;72:617–22.
68. Okada K, Matsumoto K. Effect of skin care with an emollient containing a high water content on mild uremic pruritus. Ther Apher Dial. 2004;8(5):419–22.
69. Duque MI, Yosipovitch G, Fleischer AB, Willard J, Freedman BI. Lack of efficacy of tacrolimus ointment 0.1% for treatment of hemodialysis-related pruritus: a randomized, double-blind, vehicle-controlled study. J Am Acad Dermatol. 2005;52:519–21.
70. Szepietowski JC, Szepietowski T, Reich A. Efficacy and tolerance of the cream containing structured physiological lipids with endocannabinoids in the treatment of uremic pruritus: a preliminary study. Acta Dermatovenerol Croat. 2005;13(2): 97–103.
71. Chen YC, Chiu WT, Wu MS. Therapeutic effect of topical gamma-linolenic acid on refractory uremic pruritus. Am J Kidney Dis. 2006;48(1):69–76.
72. Boaz M, Shtendik L, Oron M, Portugal-Cohen M, Kohen R, Biro A, et al. A randomized controlled clinical trial comparing the efficacy of dead sea mineral-enriched body lotion versus two types of placebo in the treatment of cutaneous dryness, itching, peeling and tightness in hemodialysis patients (EDIT). Nephron Clin Pract. 2009;113(3):c169–76.
73. Young TA, Patel TS, Camacho F, Clark A, Freedman BI, Kaur M, et al. A pramoxine-based anti-itch lotion is more effective than a control lotion for the treatment of uremic pruritus in adult hemodialysis patients. J Dermatolog Treat. 2009; 20(2):76–81.
74. Makhlough A. Topical capsaicin therapy for uremic pruritus in patients on hemodialysis. Iran J Kidney Dis. 2010;4(2): 137–40.
75. Balaskas E, Szepietowski JC, Bessis D, Ioannides D, Ponticelli C, Ghienne C, et al. Randomized, double-blind study with glycerol and paraffin in uremic xerosis. Clin J Am Soc Nephrol. 2011;6(4):748–52.
76. Castello M, Milani M. Efficacy of topical hydrating and emollient lotion containing 10% urea ISDIN® plus dexpanthenol (Ureadin Rx 10) in the treatment of skin xerosis and pruritus in hemodialyzed patients: an open prospective pilot trial. G Ital Dermatol Venereol. 2011;146(5):321–5.
77. Lin TC, Lai YH, Guo SE, Liu CF, Tsai JC, Guo HR, et al. Baby oil therapy for uremic pruritus in haemodialysis patients. J Clin Nurs. 2011;21(1–2):139–48.
78. Aramwit P, Keongamaroon O, Siritientong T, Bang N, Supasyndh O. Sericin cream reduces pruritus in hemodialysis patients: a randomized, double-blind, placebo-controlled experimental study. BMC Nephrol. 2012;13:1–11.
79. Feily A, Dormanesh B, Ghorbani AR, Moosavi Z, Kouchak M, Cheraghian B, et al. Efficacy of topical cromolyn sodium 4%

on pruritus in uremic nephrogenic patients: a randomized double-blind study in 60 patients. Int J Clin Pharmacol Ther. 2012 Jul;50(7):510–3.
80. Jung KE, Woo YR, Lee JS, Shin JH, Jeong JU, Koo DW, et al. Effect of topical vitamin D on chronic kidney disease-associated pruritus: an open-label pilot study. J Dermatol. 2015;42(8):800–3.
81. Nakhaee S, Nasiri A, Waghei Y, Morshedi J. Comparison of Avena sativa, vinegar, and hydroxyzine for uremic pruritus of hemodialysis patients: a crossover randomized clinical trial. Iran J Kidney Dis. 2015;9(4):316–22.
82. Imani NJ, Saeedi M, Hajheydari Z, Ebrahimzadeh MA, Morteza-Semnani K. Effect of Sambucus ebulus topical preparation on uremic pruritus. Pharmacheutical Biomed Res. 2017; 3(2):26–32.
83. Mehri Z, Afrasiabifar A, Hosseini N. Improved itchy quality of life following topical application of sweet almond oil in patients with uremic pruritus: a randomized, controlled trial. Jundishapur J Chronic Dis Care. 2018;7(2):1–7.
84. Yahya Y, Roiana N, Andarina R, Saleh I. Efficacy of 20% urea cream in uremic pruritus with uremic xerosis in chronic renal failure patients undergoing hemodialysis. Period Dermatol Venereol. 2018;30(1):1–9.
85. Khorsand A, Salari R, Noras MR, Saki A, Jamali J, Sharifipour F, et al. The effect of massage and topical violet oil on the severity of pruritus and dry skin in hemodialysis patients: a randomized controlled trial. Complement Ther Med. 2019;45:248–53.
86. Aquino TMO, Luchangco KAC, Sanchez EV, Verallo-Rowell VM. A randomized controlled study of 6% gabapentin topical formulation for chronic kidney disease-associated pruritus. Int J Dermatol. 2020;59(8):955–61.
87. Yoshida Y, Hirama A, Hashimoto K, Sato T, Yokota N, Saeki H, et al. Efficacy of a moisturizer for pruritus accompanied by xerosis in patients undergoing dialysis: a multicenter, open-label, randomized verification study. J Dermatol. 2021; 48(9):1327–35.
88. Lodén M. Effect of moisturizers on epidermal barrier function. Clin Dermatol. 2012;30(3):286–96.
89. Saleem MD, Maibach HI, Feldman SR. Principles of topical therapy. In: Kang S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, editors. Fitzpatrick's dermatology. 9th ed. New York: McGraw Hill Education; 2019. p. 3364–81.
90. Lodén M. Role of topical emollients and moisturizers in the treatment of dry skin barrier disorders. Am J Clin Dermatol. 2003;4(11):771–88.
91. Elmariah SB, Lerner EA. Topical therapies for pruritus. Semin Cutan Med Surg. 2011;30(2):118–26.
92. Elias PM, Sugarman J. Does moisturizing the skin equate with barrier repair therapy? Ann Allergy Asthma Immunol. 2018; 121(6):653–656.e2.
93. Draelos ZD. Active agents in common skin care products. Plast Reconstr Surg. 2010;125(2):719–24.
94. Mao-Qiang M, Feingold KR, Thornfeldt CR, Elias PM. Optimization of physiological lipid mixtures for barrier repair. J Invest Dermatol. 1996;106(5):1096–101.
95. Mao-Qiang M, Brown BE, Wu-Pong S, Feingold KR, Elias PM. Exogenous nonphysiologic vs physiologic lipids: divergent mechanisms for correction of permeability barrier dysfunction. Arch Dermatol. 1995;131(7):809–16.
96. Lodén M. The clinical benefit of moisturizers. J Eur Acad Dermatol Venereol. 2005;19(6):672–88.
97. Aresi G, Rayner HC, Hassan L, Burton JO, Mitra S, Sanders C, et al. Reasons for underreporting of uremic pruritus in people with chronic kidney disease: a qualitative study. J Pain Symptom Manage. 2019;58(4):578–586.e2.

How to cite this article: Krismi A, Danarti R, Setiabudi Ida I. Dewa Putu Pramantara, Wirohadidjojo YW. Chronic kidney disease-associated pruritus in patients undergoing hemodialysis: Xerosis and topical therapy. Hemodialysis International. 2023. https://doi.org/10.1111/hdi.13071