


# Obstacles to Early Diagnosis and Treatment of Pruritus in Patients with Chronic Kidney Disease: Current Perspectives

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**Abstract:** Chronic kidney disease-associated pruritus (CKD-aP) is a common condition amongst patients with advanced chronic kidney disease (CKD). Several studies have confirmed that more than four out of ten early-stage CKD patients suffer from this condition, while its prevalence among CKD patients on dialysis reaches up to seven out of ten. It is noted to be associated with other disabling symptoms and serious outcomes. It has significant impact on sleep, mood, daily activities, and quality of life of CKD patients, and increased mortality risk of patients on hemodialysis. The Dialysis Outcomes and Practice Patterns Study found 17% higher mortality among patients with moderate to extreme pruritus compared with patients with no or mild pruritus. Despite its high prevalence, ill-effect, and suffering associated with it, CKD-aP remains surprisingly under-reported on the patient's part and under-recognized by the healthcare team. Even upon being noticed, it remains unattended and poorly treated. Its etiopathogenesis is complex and not fully understood. Many treatment options are available but good quality evidence about most of those is absent, and to date, only two medications are approved for use in this condition. While a validated guideline is very much required for the benefit of the patients and caretakers, further research on several aspects of this issue is required.

**Keywords:** chronic kidney disease, chronic kidney disease-associated pruritus, CKD-aP, pruritus, itching, uremia, uremic pruritus

## Introduction

Chronic kidney disease (CKD) affects around 10% of the world's population. Patients with CKD suffer from several chronic symptoms and amongst these pruritus is one of the more problematic which affects their health in many ways. This article aims to provide a brief narrative review of the clinical importance of this problem, its effect on health, the obstacles in early recognition, and barriers in the evidence-based management of patients with CKD suffering from this symptom.

Pruritus or itch is a sensation over the skin or adjoining mucosal surfaces arousing a desire to scratch. Such a sensation evokes an urge or desire to scratch with sensory, emotional, and motivational components.<sup>1</sup> Whilst the itch-scratch-itch cycle can occasionally be pleasurable, it is mostly unpleasant and damaging, especially when chronic. Chronic pruritus is defined as an unpleasant sensation to the skin leading to the desire to scratch, which persists for more than six months.<sup>2</sup>

The evolution of the pruritic sensation is presumed, like pain, to be have arisen because it was protective in some way. People with congenital insensitivity to pain and itch rarely survive beyond their thirties.<sup>3-5</sup> Itch is a common symptom of many dermatological and systemic diseases, notably including CKD. Pruritus in CKD has also previously been described as uremic pruritus to which there were objections, because that suggested causality while uremia was not always associated with pruritus, and it was suggested to be amended as "uremia associated pruritus".<sup>6</sup> However the accepted term now, after the acceptance of the concept and nomenclature of CKD, is chronic kidney disease-associated pruritus

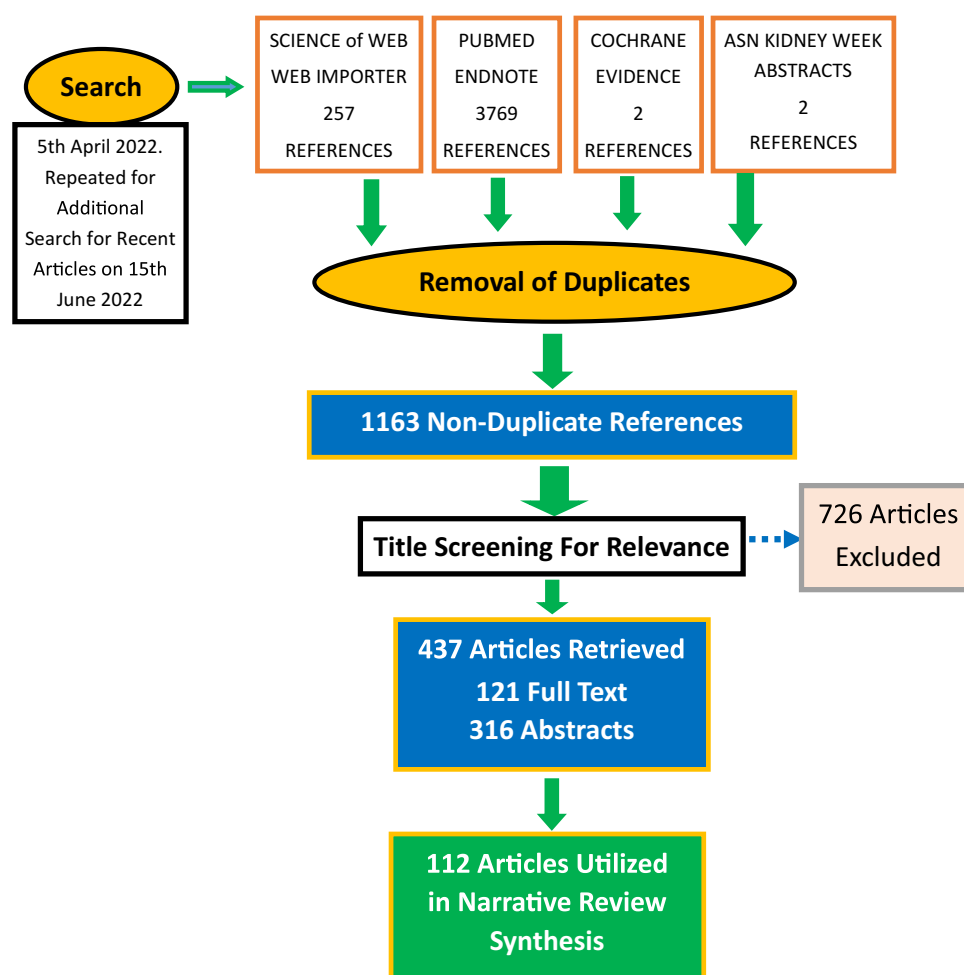
(CKD-aP). The present review will focus on understanding how important pruritus is in patients with CKD, what the difficulties are in its early diagnosis, and the challenges in its early treatment.

## Materials and Method

PubMed, Science of Web, Cochrane database and American Society of Nephrology Kidney week abstracts were searched till 5th April 2022. Search terms were “Itching in Chronic Kidney Disease”, “Pruritus in Chronic Kidney Disease”, “itching in dialysis”, “pruritus in dialysis”, “Uremic pruritus”, and “CKD-aP”. The search was repeated on 15th June 2022 to supplement recent publications after 5th April 2022. EndNote software was used to organize the references. 4030 search results yielded 1163 nonduplicate references. Titles were screened for relevance, and 437 articles were selected to retrieve 121 full text and 316 abstracts. 112 of those were utilized in the synthesis of a narrative review of the subject (Figure 1).

## CKD-aP: Importance Prevalence

In CKD patients, pruritus as an isolated symptom is uncommon whilst its presence in a cluster of two or more other symptoms together is high. Its prevalence in the different studies varies from 20% to 85%. In the earliest report, Young et al noted pruritus to be present in 85% of the small group of 36 patients on maintenance hemodialysis.<sup>8</sup> However, more recent studies suggest a much lower prevalence.



**Figure 1** PRISMA Flow Diagram of Methodology.

**Notes:** PRISMA Figure adapted from Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. Creative Commons.<sup>7</sup>

A recent prospective, observational study by Wulczyn et al found that pruritus was present in 42% of 3685 participants from the Chronic Renal Insufficiency Cohort Study (CRIC) patients with CKD not on dialysis. The severity of the symptom at baseline was reported as moderate to extreme in approximately one third of stage 1 to 3a CKD patients, and in about half of stage 3b to 5 CKD patients. The severity of pruritus increased nonlinearly with the progression of renal impairment.<sup>9</sup> A decrease in eGFR of 5 mL/min per 1.73 m<sup>2</sup> was associated with a worsening of the symptom severity score by two points or less on a scale of zero to 100 points. Uremic symptom worsening score for any degree of decrease in eGFR was greater for lower initial eGFR.<sup>9</sup>

The largest study of CKD-aP prevalence in CKD patients not on dialysis was from the USA, Brazil, and France in the international, prospective CKD Outcomes and Practice Patterns Study (CKDOPPS) comprising 67% of a nephrology-clinic based cohort of 5658 adult patients of stage 3 to stage 5 CKD not on dialysis. It found that the overall prevalence of moderate pruritus was 24% (24% in Brazil, 29% in the USA, and 23% in France), and of severe to extreme pruritus 12% (11% in Brazil, 13% in the USA, and 10% in France). The prevalence of moderate-to-extreme pruritus was higher in the advanced stages of CKD with the adjusted rate being 19% higher in stage 5 compared to stage 3 disease.<sup>10</sup>

A study of RENINE/PROMs registry data of 2978 Dutch dialysis patients by van der Willik et al revealed that 50% of patients had itching which was described as “persistent itching” by 70% of those 50%.<sup>11</sup>

For dialysis patients, data from the Dialysis Outcomes and Practice Patterns Study (DOPPS 1996–2004) revealed that more than 70% of prevalent dialysis patients had some degree of pruritus. Moderate to extreme pruritus was experienced by 42% of prevalent HD patients during 2002/2003 of the study period.<sup>12</sup> The incidence of moderate to severe degrees of pruritus in DOPPS II (2002–2004; 12 countries, 317 facilities, 10,265 patients) was 42% and in DOPPS I (1996–2001; 6 countries, 284 facilities, 10,810 patients) it was 45%.<sup>12</sup> In the DOPPS Phases 4 to 6 (2009–2018; 23,264 hemodialysis patients from 21 countries) study, 67% patients had pruritus of some degree, leaving only 33% of patients pruritus free while moderate to extreme pruritus was experienced by 37%.<sup>13</sup>

A similar (44%) prevalence of moderate to extreme degree of pruritus was self-reported in Japan (JDOPPS) from 1999 to 2008. The overall prevalence was similar in all three study phases.<sup>14</sup>

In a study of 71,012 patients who had responded to the Kidney Disease Quality of Life-36 (KDQOL) survey amongst 73,124 dialysis patients at a large dialysis organization (LDO) in the USA during January 2009 to May 2012, 60% of respondents reported itching and 14.5% of the patients reported being “very much bothered” or “extremely bothered” by itchiness.<sup>15</sup>

The ITCH National Registry Study of hemodialysis patients from the USA suggested that 84% of patients suffered from pruritus, and symptoms had been present for more than one year in 59%.<sup>16</sup>

The pooled prevalence of CKD-aP from 11 different studies in China was 61% (95% CI, 52–69).<sup>17</sup>

A cross-sectional German Epidemiological Hemodialysis Itch Study (GEHIS) in hemodialysis patients in Germany found a point prevalence of 25.2% and a lifetime prevalence of 35.2% of chronic itch.<sup>18</sup>

Gatmiri et al reported the prevalence to be 58.6% among hemodialysis patients in Iran.<sup>19</sup>

Although there is no large-scale study on CKD-aP prevalence in peritoneal dialysis patients, reporting in small studies suggests the incidence similar to that in hemodialysis.<sup>20,21</sup>

## Under-reporting

Interestingly, Rayner et al noted that among those patients who were nearly always or always bothered by itchy skin, 17% had not reported their symptoms to any healthcare provider.<sup>22</sup> So it is likely that the true prevalence of the symptom of itch in CKD patients may be much higher.

## Clinical Impact

CKD-aP cannot merely be considered only a symptom. It has been found to be associated with adverse health outcomes and higher morbidity and mortality. Reduced Health-Related Quality of life (HRQoL) in patients with CKD-aP has been noted in several studies of hemodialysis patients.<sup>12,13,16,18,20,23–28</sup> DOPPS I & II noted a 17% higher mortality risk ( $p < 0.0001$ ) for patients with moderate to extreme pruritus compared with patients with mild or no pruritus. However, this higher mortality risk lost statistical significance after adjustment for sleep quality measures, suggesting that either combination of symptoms carried higher mortality risk or higher mortality risk associated with CKD-aP is because of its effect on quality of sleep.<sup>12</sup> It remains a subject of further examination and research.

The DOPPS Phase 4–6 study showed that patients with severe pruritus had a higher rate of hospitalization and a larger number of deaths due to cardiovascular and infection-related causes compared with those with less severe symptoms. Patients extremely bothered by pruritus were also less likely to be employed, more likely to withdraw from dialysis, and more likely to miss hemodialysis sessions. There were also strong associations between pruritus severity and a number of other variables such as recovery time after a hemodialysis session, self-reported physical and mental quality of life, depressive symptoms, poor sleep quality, self-reported restless sleep, dizziness and faintness etc., all related in a monotonic mathematical fashion.<sup>13</sup> Patients extremely bothered by pruritus had a hazard ratio of withdrawal from dialysis 1.50 (95% CI, 1.05–2.14), adjusted all-cause mortality 1.24 (95% CI, 1.08–1.41), cardiovascular mortality 1.29 (95% CI, 1.06–1.57), and infection-related mortality 1.44 (95% CI, 1.05–1.96) compared with those patients not bothered at all by the symptom of pruritus.<sup>13</sup>

Mathur et al found that the intensity of itching assessed with different instruments such as the visual analogue scale (VAS), numerical rating scale (NRS), itch measurement of sleep (itch-MOS), or Self-Assessed Disease Severity etc. were all associated with lower HR-QOL in every domain measured, including sleep, mood, emotional distress, social functioning, and work etc.<sup>16</sup>

Whilst the DOPPS data suggested that the effect of severe pruritus on the mortality may be mediated through the quality and nature of sleep, a study by Narita et al of 1773 adult Japanese hemodialysis patients found that severe CKD-aP was independently associated with an increased death rate.<sup>29</sup>

Amongst the sleep disturbances recognized to be associated with CKD-aP were difficulty in falling asleep, impaired sleep quality, nocturnal wakefulness, daytime somnolence, and restless sleep etc.<sup>13,20,23</sup> In addition restless leg syndrome and chronic pain were more likely to be present in patients with CKD-aP.<sup>18,30,31</sup>

The finding of an association with increased chance of missing hemodialysis sessions noted in DOPPS 4 to 6 was also noted among Large Dialysis Organization (LDO) patients of USA together with an increase in the use of medications such as IV antibiotics, erythropoiesis stimulating agents, and IV iron.<sup>15</sup>

Thus, based on the burden of the suffering, the morbidity, the mortality, and the poor quality of life associated with the CKD-aP, it is important (importance summarized in Table 1) that itch symptom in CKD patients is looked for and addressed while caring for these patients at all stages of disease including patients on dialysis.

## Obstacles to the Early Diagnosis

Experts have described the diagnosis of CKD-aP as challenging.<sup>32</sup> There are several issues related to early diagnosis as CKD-aP may not merely be a symptom but rather a chronic systemic condition related to kidney disease, with or without any other comorbid conditions to confound the causes of itching.<sup>33</sup> The presence of comorbidities in patients with CKD which in themselves may cause pruritus makes the evaluation of CKD-aP difficult. Such comorbidities may be dermatological, hepatobiliary, hematological, endocrine, neurological, or oncological etc. In addition, such patients with CKD frequently receive a large number of medications which can cause itching, posing diagnostic uncertainty.

Additionally, there are widely variable clinical presentations of CKD-aP with symptoms that may be paroxysmal lasting from a few minutes to few hours or regular and continuous and may cause minimal disruption to complete restlessness. While the skin may be normal, xerosis cutis and dryness of the skin is observed in the majority of the patients. The absence of any primary skin lesion is common and described to be the rule but excoriation and prurigo secondary to itching might be present. Pruritus is generalized and symmetrical in about ~50% of the patients or localized to the face, arm, back, fistula arm, or lower limbs in others.<sup>16,32,33</sup> There may be chronic changes leading to crusts, papules, ulcerations, erosions, prurigo nodularis, or evidence of secondary infection such as impetigo etc.<sup>34</sup>

## Recognition

The recognition of the problem is the first step toward treatment. Given the association with negative outcomes associated with CKD-aP, the symptom of pruritus should be considered important at any time in advanced CKD (stage 5 regardless of whether on dialysis or not) and considered diagnostic of CKD-aP unless an obvious alternate cause is present.

**Table I** Importance of CKD-aP

PREVALENCE			
Nondialysis CKD Patients	Wulczyn et al <sup>9</sup> (CRIC Study)	42%	Severity increased nonlinearly with the progression of renal impairment
	CKDOPPS <sup>10</sup>	24% (23–29%)	Prevalence 19% higher in CKD5 compared to CKD3
	(RENINE/PROM) <sup>11</sup>	50%	
Hemo-Dialysis Patients	Young et al <sup>8</sup>	85%	
	DOPPS 1996–2004 <sup>12</sup> (Phase I to 3)	>70%	
	DOPPS 1996–2004 <sup>13</sup> (Phase 4 to 6)	67%	Moderate to extreme in 37%
	JDOPPS 1999 –2008 <sup>14</sup>	20–70%	Moderate to extreme in 44% (40–50%)
	LDO <sup>15</sup>	60%	14.5% very much bothered with itch
	ITCH National Registry USA <sup>16</sup>	84%	
	China: pooled prevalence from 11 studies <sup>17</sup>	61%	
	GEHIS (Germany) <sup>18</sup>	25%	Point prevalence 25.2%; lifetime prevalence of 35.2%
	Gatmiri et al (Iran) <sup>19</sup>	58%	
PD	Tessari et al (Italy) <sup>20</sup>	52%	Mode of PD not mentioned
CAPD	Mettang et al <sup>21</sup>	50%	
UNDER-REPORTING			
Rayner et al <sup>22</sup>		17% of those with severe itch never reported their symptom to healthcare provider	
CLINICAL ADVERSE EFFECTS			
Higher mortality <sup>12,13</sup>		17% higher mortality risk for patients with moderate to extreme pruritus compared with patients with mild or no pruritus	
Reduced HRQoL <sup>12–14,16,18,20,23–28,30</sup> Higher hospitalization rate <sup>13</sup> Higher withdrawal from dialysis <sup>13,15</sup> Decreased chance of employment <sup>13</sup> Restless leg syndrome, chronic pain, sleep disturbance <sup>14,18,21,30,31</sup> Increased use of medications <sup>15</sup>			

As noted above, symptom of pruritus is under-reported by CKD patients.<sup>22</sup> A factor that may be relevant in under-reporting may be the patients' lack of awareness of a link of pruritus with kidney disease, or their acceptance that itch is something they may have to live with. Other communication barriers such as the language and available length and timing of consultations, during which they may prioritize other health issues, may also be responsible factors.<sup>35</sup> Healthcare teams may also not be actively seeking these symptoms. Rayner et al found that the majority of medical directors of dialysis facilities across the globe underestimated the prevalence of CKD-aP to merely one-third to one-fifth of the true prevalence.<sup>22</sup> Zucker et al used the following criteria for the diagnosis of pruritus of CKD: 1) more than or equal to three episodes of itch during a period of 2 weeks, with the symptom appearing a few times a day, lasting at least few minutes, and troubling the patient; 2) the appearance of an itch in a regular pattern during a period of 6 months, but less frequently than listed above; and 3) absence of prolonged pruritus caused by an additional disease.<sup>36</sup>

An early diagnosis can be improved by the inclusion of pruritus-related information in pre-dialysis education of patients, the inclusion of systemic symptom assessment in routine kidney care, the use of a checklist, development of guidelines, and use of validated questionnaires in day-to-day clinical practice and quantification of the symptom.

## Obstacles to the Treatment

### Under-Recognition

Unrecognition is the first important obstacle in early management of CKD-aP. Around 17% of patients who were nearly always or always bothered by itch had not reported their symptoms to any healthcare provider. This was higher in the USA (33%), compared to the Gulf Cooperation Council countries (12%), and variable in Europe, where it varied from 21% in Sweden to 8% in Italy.<sup>22</sup> This under-reporting on the part of the patients was supplemented by underestimation of the symptom burden by clinicians involved in their care. In a large fraction of facilities where one-fifth to half of the patient population had severe pruritus, only 1% of the medical directors were able to estimate the exact prevalence of the pruritus. Around two-thirds of medical directors estimated that <5% of their patients had severe pruritus while the true prevalence of severe pruritus was 13 to 26%. Additionally the patients were more likely to report the symptom of pruritus to a nephrologist and dialysis staff members than to a dermatologist or primary care physician.<sup>22</sup>

The use of a checklist and symptom scoring system can help in early recognition of pruritus. For example, Integrated Palliative care Outcome Scale (IPOS-renal) contains a question about itching.<sup>37,38</sup> When regularly applied to patients this may help patients report and identify issues.

### Ignored Symptom Cluster

The second obstacle to the treatment lies in our approach to addressing the pruritic symptom individually instead of recognizing it as a component of other related issues which could exert the synergistic effects upon each other resulting in the amplified suffering of the patient. More recently the occurrence of such related symptoms together referred to as a “symptom cluster”, causing *synergistic* effects, and where treatment of one of those symptoms may affect the others and the outcome, has been recognised<sup>39,40</sup> (Table 2). Addressing identified modifiable risk factors associated with CKD-aP should also be the part of a strategy of the management of CKD-aP. Symptom clusters may have a common pathological mechanism, the management of which may bring broader involvement and effect.<sup>41</sup> Understanding about the science of the symptom cluster at present is not evolved much, less so in the area of CKD. It requires a change in our outlook and more research in this area of CKD is needed.<sup>42</sup>

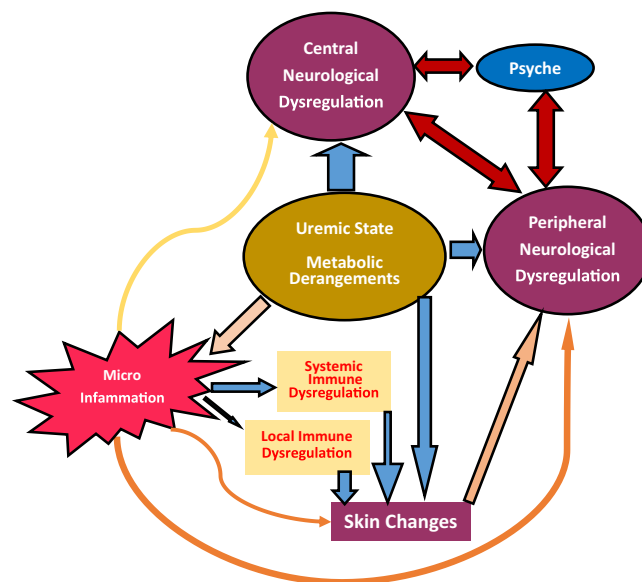
### Pathogenesis

The third obstacle to treatment lies in our inadequate current understanding of the pathological mechanism of the CKD-aP which is based upon pieces of information derived from association and intervention. It lacks comprehensive nature. A brief view of it may illustrate the limitation of the different treatments of CKD-aP which limits effectiveness of our approach to treatment. The pathogenesis of CKD-aP is multifactorial, with roles of metabolic derangements in uremia,

**Table 2** Symptom-Cluster of CKD-aP

<b>Itching</b>
<b>Depression</b>
<b>Anxiety</b>
<b>Stress</b>
<b>Fatigue</b>
<b>Pain</b>
<b>Sleep disturbances</b>
<b>Restless leg syndrome</b>
<b>Post-dialysis fatigue</b>





**Figure 2** Pathogenic factors of CKD-aP and their interactions.

immune dysfunction, microinflammation, histological changes in the dermis, and alterations in receptors as well as dysregulation in peripheral and central nervous system, endogenous opioid systems, and the psyche etc. (Figure 2).

### Metabolic and Uremic

Uremic metabolic derangements likely lie at the center of the issue and an important reciprocal relationship between urea clearance ( $kt/v$ ) and incidence of CKD-aP exists in dialysis patients.<sup>43,44</sup> Wulczyn et al noted that in patients not on dialysis a decrease in eGFR of 5 mL/min per 1.73 m<sup>2</sup> was associated with a worsening of the symptom severity score by two points or less on a scale of zero to 100 points. Uremic symptom worsening score for any degree of decrease in eGFR was greater for lower initial eGFR.<sup>9</sup> Transplantation dramatically reduces the prevalence and intensity of CKD-aP to ~12% (versus 35% controls) with reversal of skin histopathological changes observed in CKD-aP.<sup>45</sup> Different accumulated toxic metabolites or deranged levels of nontoxic metabolites may act as pruritogens or modify the itch perception mechanism. Hsu et al associated a higher serum aluminum levels with a higher prevalence of CKD-aP.<sup>46</sup> Parathyroidectomy was noted to be an effective therapy in a group of patients with CKD-aP, although not always.<sup>47</sup> An elevated calcium phosphate product and elevated parathyroid hormone level in the group of patients who benefitted from parathyroidectomy suggests that CKD mineral bone disease may be a factor related to CKD-aP.<sup>11,12</sup> However the calcium phosphate product is an artificial construct and unlikely to be highly representative in the complex physiology of mineral trafficking and it is highly likely that the subtleties of mineral trafficking have been missed by the crude association of the calcium phosphate product. Nevertheless, there is more calcium in the basal skin layer in patients with CKD-aP and this is an area that needs further research.<sup>48,49</sup>

Hiroshige et al in their prospective study found that good dialysis and a good nutritional status reduced the prevalence and degree of pruritus in the patients with disabling symptoms but without significant disorders of calcium and phosphate metabolism. Significantly higher values of blood urea nitrogen (BUN) and plasma beta 2-microglobulin pre-dialysis were observed in those pruritic patients with lower dialysis dose estimated by  $Kt/V_{urea}$  and normalized protein catabolic rate (nPCR).<sup>50</sup> Wu et al compared serum metabolic profiles of severely pruritic patients against mildly pruritic patients with uremia using ultra-performance liquid chromatography–quadrupole time-of-flight mass spectrometry (UPLC-QTOF MS) and identified nine candidate biomarkers which belonged to chemical groups of phospholipids, uremic toxins, and steroids.<sup>51</sup> The role of accumulated mid and large molecules in the causation of CKD-aP is supported by a randomized, prospective, double-blind study comparing the effect of high permeability hemodialysis (HPHD) against conventional hemodialysis (CHD) on CKD-aP by Chen et al which showed that the degree of itching in the trial group (HPHD) was significantly lower than that in the control group ( $2.23 \pm 1.05$  vs  $5.45 \pm 1.91$ ,  $P=0.009$ ) as measured by visual analogue

scale (VAS) of itching.<sup>52</sup> Lim et al compared the effect of dialysis with a medium cut-off (MCO) dialyzer to that with high-flux dialyzers on quality of life outcomes in maintenance hemodialysis patients. Their finding was that dialysis with MCO dialyzers improved physical functioning and reduced the scores for morning pruritus distribution and the frequency of scratching during sleep.<sup>53</sup>

### Microinflammation and Dysregulated Immune Function

There is also a probable role of microinflammation and dysregulated immune function in patients with CKD-aP. This dysfunction appears to be both at the systemic level and local dermatological levels. A few risk factors such as white blood cell (WBC) count  $>6700/\mu\text{L}$ , or the presence of hepatitis C or ascites associated with severe pruritus identified in the DOPPS study suggest the role of microinflammation.<sup>11</sup> Additionally, significantly raised blood levels of cytokines may play a key role in CKD-aP including Interleukin-31 (IL-31), Interleukin-6 (IL-6), and Interleukin-2 (IL-2) as well as other evidences of immune activation or dysregulation such as raised Th1 lymphocytes or C-reactive protein (CRP).<sup>54,55</sup>

In comparison to patients without pruritus, itching patients have been noted to have significantly higher dermal mast cell counts which were mainly degranulated and diffusely spread, as well as an increased ratio of Th1:Th2 T cells with higher circulating level of histamine, serotonin, tryptase, and other interleukins.<sup>21,55–58</sup> Whilst the antihistamines and serotonin receptor inhibitor ondansetron has not shown therapeutic benefit, the mast cell stabilizer cromolyn and leukotriene receptor antagonist Montelukast have shown benefit in the relief of CKD-aP. Tacrolimus which blocks calcineurin mediated IL-2 production from helper T cells has shown therapeutic benefit in a few studies.<sup>21,59–62</sup>

The seemingly unconnected observation that patients on hemodialysis receiving a statin appear to suffer less from pruritus is also suggested to be due to its ability to lower serum proinflammatory cytokines and CRP.<sup>63</sup>

Metabolic derangements of CKD with systemic microinflammation bring multiple skin changes such as dryness, xerosis, increased number of dermal mast cells, secretion of pruritogens from local dermal mast cells, deposition of calcium and magnesium micro-crystals, and the proliferation of nerve fibers etc., which are considered contributive to cause pruritus.

### Dysregulation of Nervous System

Neural itch pathways at the central and peripheral levels are becoming better understood.<sup>64–67</sup> There are mechano-sensitive and mechano-insensitive C-fibers that respond differently to histamine or other pruritogens such as cowhage.<sup>68</sup> Microneurography of human skin nerves has demonstrated that itch induced by different agents activates different neuronal populations in the peripheral nervous system (PNS).<sup>69</sup> Additionally, most CKD patients have altered skin innervation with abnormal neuron-specific enolase (NSE)-immunoreactive nerve terminals and fibers sprouting throughout the layers of the epidermis in patients on maintenance hemodialysis.<sup>70,71</sup> A peripheral neuropathic mechanism is suggested by therapeutic relief by gabapentin and pregabalin which have proven beneficial effects in the treatment of neuropathic pain.<sup>72–74</sup> There is also emerging evidence around a dysregulated endogenous opioid system being causative or contributory to CKD-aP.<sup>75</sup> There are three endogenous opioid receptors,  $\mu$ -opioid receptor (MOR),  $\kappa$ -opioid receptor (KOR), and  $\delta$ -opioid receptor (DOR), whose corresponding endogenous ligands are endorphins, dynorphins, and enkephalins respectively, which are present in the central nervous system as well on peripheral nerve fibers. Evidence suggests that the KOR system suppresses itch whilst the MOR system stimulates itch.<sup>76</sup> MOR overactivity, KOR underactivity, or antagonism would act synergistically to promote itch. The finding of an increased ratio of MOR agonist  $\beta$ -endorphin to KOR agonist Dynorphin A in hemodialysis patients with CKD-aP is suggestive of such a mechanism.<sup>77</sup>

### Treatment Options and Limitations

There is a general dearth of high-quality evidence around treatment for CKD-aP together with the absence of a systematic approach to therapy. Although there is plenty of anecdotal literature on treatment options which have been used in several small trials or case series, very few of those have adequate power or quality, and there are no international guidelines or validated algorithms available to use those effectively. Expert opinion-based algorithmic approaches have been suggested by several authors in review articles and a stepwise approach is suggested by Patel et al.<sup>32,78–80</sup> The treatments advocated



**Table 3** Various Treatments Used in CKD-aP

Mode	Effective	Not Effective or Variable Effect
<b>Topical</b>	<ul style="list-style-type: none"> <li>• Emollients with high water content</li> <li>• Emollients with natural lipids and endocannabinoids</li> </ul>	<ul style="list-style-type: none"> <li>• GLA-rich 2.2% cream/primrose oil</li> <li>• Dead Sea lotion</li> <li>• Pramoxine HCl 1% lotion</li> <li>• Tacrolimus 0.1% ointment thrice weekly</li> <li>• Chinese herb-based cream Capsaicin 0.025% cream</li> <li>• Sarna lotion</li> <li>• Avena sativa lotion</li> <li>• Cromolyn sodium 4%</li> <li>• Lidocaine</li> </ul>
<b>Physical</b>	<ul style="list-style-type: none"> <li>• Narrow-band UVB</li> </ul>	<ul style="list-style-type: none"> <li>• Far-infrared ray</li> </ul>
<b>Systemic</b>	<ul style="list-style-type: none"> <li>• Pregabalin</li> <li>• Gabapentin</li> <li>• Difelikefalin: 0.5 µg/kg IV thrice weekly</li> <li>• Nalfurafine HCl 5 µg OD or 5 µg IV post-HD 3×/week</li> <li>• Butorphanol 1 mg OD intranasally</li> </ul>	<ul style="list-style-type: none"> <li>• Ondansetron 8 mg TDS</li> <li>• Naltrexone 50 mg OD</li> <li>• Montelukast</li> <li>• Nicotinamide 500 mg BID</li> <li>• Oral Zinc sulfate</li> <li>• Oral cromolyn sodium 135 mg TDS</li> <li>• 2 GLA-enriched evening primrose oil capsules BID</li> <li>• Thalidomide 100 mg OD</li> <li>• Cholestyramine 5 g BID</li> <li>• Oral charcoal</li> </ul>
<b>Intervention</b>	<ul style="list-style-type: none"> <li>• HFHD; HDF; MCO dialyzers</li> <li>• High-permeability HD</li> <li>• Renal transplant</li> </ul>	<ul style="list-style-type: none"> <li>• Mg-free dialysate</li> <li>• Parathyroidectomy</li> </ul>
<b>Empirical</b>	<ul style="list-style-type: none"> <li>• Acupuncture</li> </ul>	<ul style="list-style-type: none"> <li>• Auricular acupressure</li> <li>• Chinese herb</li> </ul>

**Abbreviations:** HFHD, high flux hemodialysis; HDF, hemodiafiltration.

can be broadly classified into topical, systemic, physical, and empirical (Table 3). Simonsen et al have performed a systematic review of these treatments but found that the majority of those studies lacked quality due to flawed technology, small sample sizes, or heterogeneity.<sup>81</sup> At present there are only two drugs approved for the treatment of CKD-aP: selective peripheral KOR agonist Nalfurafine approved in Japan and selective peripheral KOR agonist Difelikefalin approved by the FDA, USA.<sup>82–85</sup>

## Clinical Evaluation

A regular periodical evaluation plan for CKD-aP should be available in CKD and dialysis clinics with elements including history, examination, investigation, evaluation of quality of life (QOL), sleep assessment, severity scoring of pruritus, and assessment of modifiable risk factors (Table 4), and the presence of the symptom cluster (Table 2). A validated symptom scoring system should be used to guide the management more objectively. A salient clinical evaluation should focus upon:

- The history to gather information about the location, severity, duration, character, frequency, and exacerbating and relieving factors of the pruritus.
- A system review to note presence of systemic diseases, review of the drug history, and smoking status should form a central part of evaluation.
- Every patient with advanced CKD should be evaluated for sleep, its quality, and for depression and anxiety.

**Table 4** Risk Factors and Hazard Ratio of Moderate to Extreme CKD-aP

Risk Factors and HR of Moderate to Extreme CKD-aP*	
• Male (vs female)	1.10
• Ascites (vs no)	1.85
• Hepatitis C (vs no)	1.29
• WBC count >5400/mL	1.03–1.2
• Serum phosphorus, >5.5	1.2–1.37
• Corrected serum calcium >10.2 g/dl	1.22
• Serum ferritin <100 ng/mL (vs 100–399 ng/mL)	1.03
• Smoking (current or stopped smoking <1 year)	1.15
• Systemic diseases – lung, neurological, CHF	
• Serum albumin, <3.0 (vs. 3.51 - 4 g/dl)	1.17
• Older age, per 10 years older	1.04

**Notes:** \*Based on DOPPS I & II.

**Abbreviations:** CHF, congestive heart failure; HR, hazard ratio.

- Examination should note excoriation marks, xerosis (dryness) of skin, prurigo nodularis, lichenification etc., which as being a sign of CKD-aP might be an alert for a primary dermatological condition for which a note should be made of.
- Evaluation of if a primary dermatological condition – a comorbidity – could be a possible cause of itching rather than CKD, including low threshold for referral to dermatologist should be practiced. However, the treatment for CKD-aP should not be delayed pending evaluation.
- Signs of heart failure and ascites which are recognized risk factors (Table 4).
- Blood tests to establish CKD stage, CRP, hemoglobin, white cell count, calcium, phosphate, albumin, PTH, hepatitis serology, aluminum level, ferritin level etc.

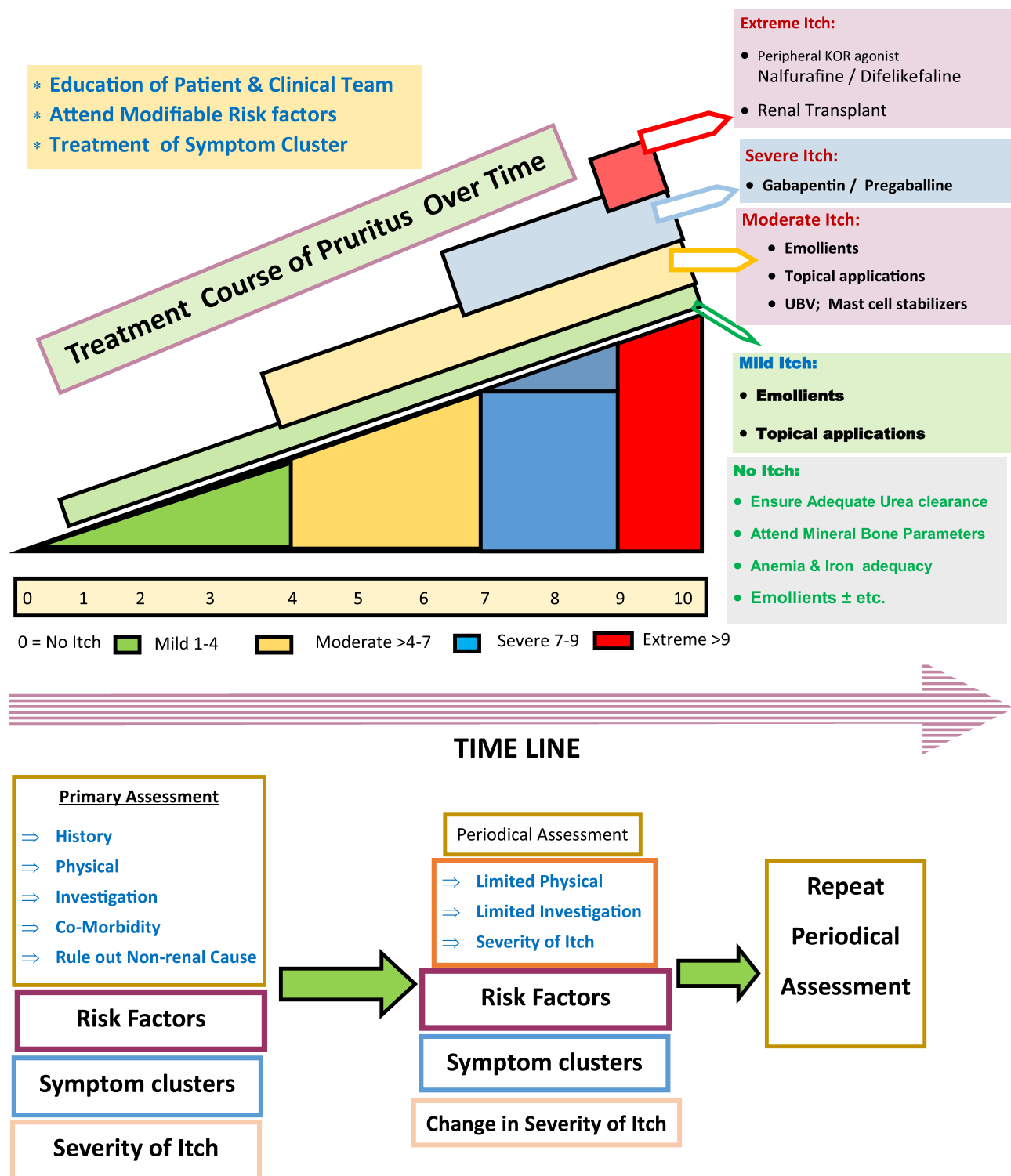
## Severity Assessment

Quantification of symptoms and QOL brings objectivity in the management. Currently used assessment tools can be divided into: 1) scales measuring the severity of the itching only; 2) multidimensional pruritus scale which measures several components of pruritus; and 3) multidimensional scales which measure the severity of itching and its impact upon the quality of life.

There are four severity measuring scales: 1) the most commonly used visual analog scale (VAS); 2) the numeric rating scale (NRS); 3) the verbal rating scale (VRS); and 4) the Kidney Disease Quality of Life-Short Form (KDQOL-SF).<sup>86</sup> VAS uses a horizontal or vertical line in which the extreme left or lowest point represents no itching and the extreme right or top the worst. NRS is similar to VAS where the severity is measured on a numerical scale from zero to ten. The verbal rating scale (VRS) has four severities of itching – no, low, moderate, or severe.<sup>87</sup> One question in the KDQOL-SF survey assesses the itching severity.<sup>88</sup> Multidimensional itching scale measures several components of the pruritus. There are two such scales, 5-D itching scale and the itching severity scale (ISS).<sup>89,90</sup> The 5-D itching scale evaluates the five domains of itching, the degree, duration, direction, disability, and distribution. The itching severity scale (ISS) measures the duration, frequency, pattern, intensity, treatment, symptoms, sensation, and effect of itching on QOL and is a valid and reliable measure of itching.<sup>90</sup> The dermatology QOL index (DLQI) and the Skindex measure the impact of skin disease on QOL. For day-to-day clinical use, the simple severity measuring scales VAS or NRS are excellent useful tools.

## Treatments

Whilst CKD is a global problem, the various treatments used for CKD-aP may not be available everywhere. In view of this it would be helpful to simplify the management plan in a stepwise manner using the most effective and least invasive treatments first. We shall briefly review a few treatment options that are generally safe and effective followed by how to use those in a real management plan (Table 3 and Figure 3).



**Figure 3** Clinical management of CKD-aP.

### Risk Factors

Several studies have identified risk factors associated with higher prevalence and serious outcome of CKD-aP (Table 4). Addressing dialysis adequacy and/or increasing dialysis time is often a good empirical first step yet there is no evidence that intensifying dialysis beyond recommended  $Kt/V$  values may have any beneficial effect. One

randomized trial examined the effect of dialysis dose upon CKD-aP and noted benefit of mean kt/v 1.28 compared to mean kt/v of 1.09.<sup>50</sup> However another nonrandomized study has noted increased risk of CKD-aP with higher dose of dialysis (kt/v 1.82).<sup>63</sup>

Attention to CKD mineral bone diseases (CKD-MBD) to control the parathyroid hormone level and calcium levels constitutes a very wide target. Serum phosphate control is frequently difficult to achieve without increasing time on dialysis. Correction of iron deficiency and anemia is also important. Stopping smoking is clearly advisable on several grounds. High flux hemodialysis (HFHD), hemodiafiltration (HDF), and high permeability hemodialysis have been linked with improved symptom of pruritus.<sup>50,91</sup> The use of magnesium-free dialysate has not brought beneficial effect.<sup>92</sup> Although the low ferritin is noted to be a risk factor of CKD-aP, we do not know if iron administration would benefit CKD-aP.

Gut binding of various uremic toxins with unpleasant activated charcoal and or cholestyramine may require more evidence to be recommended but has some logic and can be tried in patients with poor symptom control.<sup>93,94</sup>

### Topical Treatment and Emollients

Xerosis is noted in about 85% of patients with CKD-aP which is believed to add to the intensity of itch. Emollients often improve symptoms and have few downsides. It should be considered first-line treatment of xerosis.<sup>95</sup> There is no evidence as to whether preemptive use of emollients in patients with advanced CKD without itch or xerosis could be effective. Topical preparation containing structured natural lipids and endocannabinoids have been reported to be effective in controlling pruritus and xerosis in maintenance hemodialysis patients.<sup>96</sup> A multicenter double-blind, randomized controlled trial of 100 dialysis patients with moderate to severe uremic xerosis randomized to glycerol 15% and paraffin 10% in an oil-in-water emulsion versus an oil-in-water emulsion alone, showed benefit to the former preparation.<sup>97</sup> Evidence regarding benefit of topical application of Tacrolimus is contradictory in different studies. Kuypers et al found topical Tacrolimus application effective in reducing symptom of pruritus.<sup>62</sup> However, in another study it was noted ineffective compared to placebo.<sup>98</sup>

### Antihistamines and Immunomodulation

Antihistamines are noted to be the most commonly prescribed medicines.<sup>22,34</sup> DOPPS data showed that prescription or nonprescription (over the counter) oral antihistamines were used on 57% of first-line therapies by Medical Directors of dialysis units.<sup>22</sup> Interestingly and paradoxically, antihistamines are the least evaluated in the treatment of CKD-aP. A few small studies suggest antihistamines ineffective or least effective in CKD-aP. A survey study by Gilcrest et al of 237 patients undergoing maintenance hemodialysis noted that topical emollients and orally administered antipruritic agents provided relief in only 33 (18%) and 31 (17%) patients respectively, thus specifically suggesting that antihistamines were not more effective than emollients.<sup>34</sup> Weisshaar et al tested 11 patients on hemodialysis against ten healthy controls to evaluate the effect of the 5-HT<sub>3</sub> receptor antagonists tropisetron 5 mg and ondansetron 8 mg and the antihistamine cetirizine 10 mg. Their finding was that while these medicines were able to prevent itching in normal individuals, that effect was lost in patients of CKD-aP.<sup>99</sup> Desloratadine 5 mg thrice weekly was compared with gabapentin 300 mg thrice weekly by Marquez et al in a prospective, open-label, cross-over clinical trial in 22 patients on chronic hemodialysis with sustained pruritus over a period of at least 60 days, and found Desloratadine to be effective and more tolerable.<sup>100</sup> In the absence of a proper evaluation of antihistamines in CKD-aP, several reviewers on this topic have simply repeatedly mentioned that antihistamines were not effective.<sup>32,78–80,101,102</sup> However, if effective, it might suggest the cause of itching a primary dermatological condition or an etiology other than CKD-aP. It has also been suggested that any benefit of antihistamines in ameliorating CKD-aP is possibly due to their sedative effects.

The mast cell stabilizer Cromolyn as topical 4% cream and systemic administration has been noted to be effective while nicotinamide was not found effective.<sup>60,102,103</sup> Systemic use of cromolyn should be considered in patients with high WBC count and/or elevated CRP without any evident source of infection. UVB phototherapy believed to act on mast cells locally has been found to be effective in few studies.<sup>103–105</sup> Its side effect of sun burn and tanning are recognized while long-term safety is undetermined.

### Neuroanalgesics

Gabapentin and pregabalin are two effective drugs found to be effective in the control of symptoms of CKD-aP. Their effectiveness has been confirmed in several studies and meta-analyses. However the numerous side effects such as somnolence, dizziness, dry mouth, and weight gain are a significant disincentive to their use.<sup>106–109</sup>

### Drugs Acting Upon Opioid Receptors

MOR overactivity increases pruritus but MOR antagonist naloxone and naltrexone were found ineffective in some studies.<sup>110,111</sup> However, the peripheral KOR receptor agonist Nalfurafine licensed in Japan for CKD-aP in the dose of 2.5–5 µg daily has been found effective in the control of the symptoms.<sup>84,85,111</sup> The peripheral KOR receptor agonist Difelikefalin approved for CKD-aP by the FDA administered IV in a dose of 0.5 µg/kg of body weight three times in a week has been shown to improve pruritus and quality of sleep, and its efficacy was maintained over a year.<sup>83,112,113</sup>

## Clinical Treatment Plan

In the absence of validated guidelines and the different algorithms suggested by different experts, we recommend the following treatment plan in the light of the available evidence (Figure 3):

- Education and awareness of patients and caretakers.
- Identification and treatment of risk factors.
- Optimization of dialysis adequacy.
- Prioritization of kidney transplantation where possible.
- Continuous periodical evaluation as described above in the section “Clinical Evaluation”.
- Use of emollients and topical treatments.
- Systemic use of Gabapentin or Pregabalin if the symptom is more than moderate.
- Peripheral KOR agonist for severe and extreme pruritus.

## Hemodialysis Patients: A Special Group

The patients receiving hemodialysis constitute a special group as they have higher incidence and prevalence of CKD-aP of more severe degree. These patients have frequent interaction with the medical team which provides enhanced opportunities for early detection, frequent assessment, and better management as well as research opportunities. In spite of the fact that CKD-aP is associated with higher mortality, its management rarely ranks highly in “quality of care” assessment whilst the anemia management, bone mineral management, and dialysis adequacy are often accounted. Thus, it would be important for the dialysis unit to develop and adopt a CKD-aP policy. Suggested measures would be:

- (I) Separate periodical nursing evaluation and physician’s evaluation of CKD-aP should be in a regular management plan. A local flow chart should be developed and maintained.
- (II) Antihistamines should be avoided because of paucity of evidence for benefit in this condition and higher risks of sedative effect in a uremic state.
- (III) Dialysis adequacy should be ensured.
- (IV) High flux hemodialysis (HFHD), hemodiafiltration (HDF), high permeability hemodialysis, and use of MCO dialyzers should be considered within budgetary limits, if not being used.
- (V) Smoking cessation should be promoted.
- (VI) Other symptom cluster issues should be addressed.
- (VII) Transplant should be prioritized in severe cases.
- (VIII) Research should be directed toward this patient group in order to understand and treat this disabling symptom.

## Conclusion

CKD-aP is a common symptom in advanced stages of CKD which is associated with considerable suffering, decreased HRQoL, serious outcomes, and increased mortality necessitating its early diagnosis and management. Paradoxically in

**Table 5** Areas of Research

- Identification of modifiable risk factors
- Whether the use of preemptive emollients would benefit in delaying the development of CKD-aP
- Recognition of optimal dialysis dose
- If different dialyzer membranes have any benefit
- Research in the area of the symptom cluster
- Whether calcimimetics have any beneficial role
- Long-term risk versus the safety of UVB therapy
- When to use antihistamine drugs and how long
- Burden in early CKD stages
- Development of guidelines
- Epidemiology of pruritus not due to CKD-aP in CKD patients
- How to bring helpful practice patterns

clinical practice it commonly goes unidentified and untreated because of various factors on the part of patients as well as the clinicians and knowledge gap. Its evaluation and management is complex and challenging. International Guidelines and a validated treatment algorithm are needed. Several aspects of this problem remain as knowledge gaps and should be a priority area of research (Table 5). The condition CKD-aP should be considered for a separate diagnostic code from the International Classification of Diseases (ICD). In the absence of international guidelines, institutional policies should be developed to increase awareness, early recognition, and management tailored to the locally available resources.

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