

4 Pathological Pillars/Axes of CKD-aP

1. Uremic axis

- Uremic toxins accumulate in the plasma of patients with CKD
 - **No crystals found in skin biopsies**
- DOPPS survey found **no association** between pruritus and phosphorus-calcium metabolism

2. Peripheral neuropathy

- Histamine pathway **NOT involved**
- Other pathways **overexpressed** and **overactivated**



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3. Opioid receptors

- κ (kappa) receptors – anti-pruritogens
- μ (mu) receptors – pro-pruritogens
- Located on nerve fibers
- **Imbalance** in favor of μ (mu) receptors

4. Immune system

- Opioid receptors located on immune cells



Prevalence of CKD-aP

- Moderate to severe pruritus affects **25% - 50%** of patients on hemodialysis
- In a DOPPS study, **17% of patients** were **nearly always bothered by itching** but did not report to HCPs
- **69%** of medical directors **underestimated** prevalence in hemodialysis units

Underestimated and Underreported Diagnosis



Clinical Presentation of CKD-aP

- Itch can be generalized or localized



Itch scratch marks
Credit: Dr. Antoine Lanot



Prurigo nodularis
Credit: Dr. Antoine Lanot



Impact of Itch on Patients' Lives

- **Worse health-related quality of life**
- **Physical** and **mental** burden
 - Depression
 - Embarrassment
 - Concentration difficulties
 - Work difficulties
 - Avoid interacting with people
 - Sleep disturbances
 - Daytime sleepiness
 - Unable to work
 - Can't focus on family and friends



Itch Severity and Quality of Life Assessment Tools

- Worst Itch Numerical Rating Scale (WI-NRS)

Please rate the itching severity due to your psoriasis by circling the number that best describes your worst level of itching in the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10

0 = No itching

10 = Worst itch imaginable

- In the clinical setting, the “best test is a simple test”
- Validated in KALM studies
 - **≥3-point improvement** = clinically meaningful improvement with difelikefalin
- Skindex-10 quality of life (QoL) assessment tool



Self-Assessed Disease Severity (SADS)

- Simple questionnaire
- Easy to use in clinical practice
- Allows patients to categorize themselves into 1 of 3 patient scenarios:
 - Patient A: no problem with itching
 - Patient B: moderate problem with itching
 - Patient C: very bothered by itching in several ways
- Good correlation with other scales for QoL assessment

Which of these patients are you most like? (Mark one)

Patient A

- I do not generally have scratch marks on my skin
- I do not generally have a problem sleeping because of itching
- My itching does not generally make me feel agitated or sad

Patient B

- I sometimes have scratch marks on my skin
- I sometimes have problems sleeping because of itching
- My itching does not generally make me feel agitated or sad

Patient C

- I often have scratch marks on my skin that may or may not bleed or get infected
- I often have a problem sleeping because of itching
- My itching often makes me feel agitated or sad



CKD-aP Treatment

Universal Approaches	Itch-Specific Treatment
<ul style="list-style-type: none">• Ensure adequacy of dialysis• Optimize PTH, calcium, and phosphate homeostasis <hr/> <p>Lack of evidence for itch improvement</p>	<ul style="list-style-type: none">• Difelikefalin: selective kappa-opioid receptor agonist<ul style="list-style-type: none">▪ First and only FDA-approved prescription treatment for moderate to severe CKD-aP in adults undergoing hemodialysis
<ul style="list-style-type: none">• Skin moisturizers daily to twice daily<ul style="list-style-type: none">▪ Especially after showers/baths	<ul style="list-style-type: none">• Peripherally acting opioid (no dependence liability)



Use of Antihistamines in CKD-aP

- Lack of evidence for their effectiveness
- Histaminergic pathway is **NOT involved** in CKD-aP
- **Sedation** is the main side effect

Antihistamines are NOT a recommended treatment for CKD-aP



Use of Centrally Acting Opioids in CKD-aP (eg, Fentanyl and Tramadol)

- **Centrally acting** opioids (ie, brain-accessible)
- Used to treat **peripheral neuropathy** (pain)
- Potential for drug **dependency** and **abuse**
- Adverse effects:
 - Sedation
 - Dysphoria
 - ↑ Suicidal risk



Use of Gabapentinoids in CKD-aP

Gabapentin and Pregabalin (off-label)

- **Narrow** therapeutic index
- Adverse effects
 - Dizziness
 - Somnolence
 - Weight gain
 - ↑ Suicidal risk
- Excreted by the kidney
 - **Difficult to manage dosing in patients on hemodialysis**

Adverse effects of gabapentinoids limit their use in CKD-aP



Kappa-Opioid Receptor Agonist Therapy in CKD-aP

Difelikefalin

- KALM-1 and KALM-2 trials showed a **clinically meaningful improvement in itch intensity and itch-related QoL** in patients with CKD-aP undergoing hemodialysis treated with difelikefalin

Reduction in WI-NRS score according to change perceived by patients

