SHORT COMMUNICATION

Chronic Prurigo: Current Knowledge, Treatment Strategies, Future Perspectives, and Unmet Needs

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Chronic prurigo (CPG) is a neuroinflammatory and fibrotic skin condition characterized by chronic pruritus lasting more than 6 weeks, and multiple pruriginous lesions (localized or generalized) directly associated with persistent scratching behaviour (1). Its pathophysiology involves immune dysregulation, neurogenic inflammation, and impaired skin barrier function. Some of the central cytokines implicated in CPG pathogenesis include interleukin (IL)-31, IL-4, and IL-13, which mediate itch and inflammation. Neuronal sensitization, disturbed neuroanatomy, and increased nerve growth factor expression further sustain the characteristic itch–scratch cycle (2, 3)

CPG encompasses various clinical presentations characterized by symmetrically distributed pruriginous lesions, skin-coloured, pink or red papules, nodules, or plaques. These are often hyperkeratotic, excoriated, crusted, or scaling, with a clear centre and hyperpigmented border. Five clinical subtypes exist, the nodular one (prurigo nodularis – CPGN) being the most frequent.

Clinical burden is considerable, as patients often report impaired sleep, anxiety, depression, social isolation, and reduced quality of life (5–7).

CPG patients display distinct endotypes, including predominant Th2 and Th17/Th22 inflammatory signatures, which can theoretically guide in individualizing the treatment (4). It is frequent for patients to suffer from comorbidities such as atopic dermatitis, chronic kidney disease, liver disease, diabetes mellitus, psychiatric disorders, and neurological conditions like peripheral neuropathy. There is also evidence of a significantly higher rate of mortality, mostly related to chronic ischaemic heart disease. Comorbidity clusters may influence disease course and treatment effectiveness and safety (5–8). CPG is also associated with increased healthcare resource use and higher all-cause mortality (8).

The management of CPG is complex, often requiring tailored therapeutic approaches. Guidelines advocate for a dual strategy, addressing both the neural and the immunological alterations. The United States consensus is a practical guide based on literature and experts' experience (9), whereas the IFSI guideline is a more structured paper with an integrated approach to tackle not only itch but also pruriginous lesions and the possible underlying pruritic conditions (2).

These disparities reflect differences in therapeutic preferences and access to treatments. For example: the US consensus often prioritizes earlier use of biologics when accessible, whereas IFSI maintains a stepwise escalation through neuromodulators and phototherapy before biologics; differences in access can delay initiation of biologics in some European settings compared with the United States; and IFSI places greater emphasis on aetiologic assessment and interdisciplinary management of chronic pruritus, while the US consensus is more pragmatic and PN-focused for everyday practice.

Classical immunosuppressants such as methotrexate and cyclosporine have been widely used, despite lacking formal approval for this indication, highlighting the clear need for more targeted and licensed treatment. Recently, therapeutic options have significantly expanded. Dupilumab and nemolizumab have both been approved based on robust phase 3 trial data demonstrating efficacy in itch reduction and lesion improvement (10, 11). Real-world studies further confirm dupilumab's effectiveness, underscoring substantial clinical experience (12). Additional promising treatments in development include JAK inhibitors (ruxolitinib, abrocitinib, upadacitinib, tofacitinib, and povorcitinib) (13) anti-OSMRβ antibodies such as vixarelimab (14), and anti-OX40 antibodies like rocatinlimab (15), highlighting continued exploration of novel immunological targets.

However, significant knowledge gaps remain.

Population-based database studies already quantify the burden of CPG. They show excess comorbidity, higher healthcare use, and increased all-cause mortality. This makes harmonized case definitions beyond the nodular phenotype, robust incidence estimates, and cross-country comparability including primary-care capture immediate priorities (7, 8).

Phase-3 trials have established the efficacy of blocking IL-4Rα and IL-31RA. The agenda now is long-term durability for at least 2–3 years, sequencing or combination of neural and immunologic strategies, head-to-head comparisons, and withdrawal and re-treatment designs (10, 11).

Real-world cohorts support dupilumab's effectiveness to roughly 12–18 months. We need predictors of non-response or relapse, dose or interval optimization, and drug survival data in older and comorbid patients (12).

PRO and qualitative studies document sleep disruption, anxiety or depression, and social isolation. Trials should include standardized sleep and mental-health endpoints, and services should embed mental-health support (5, 6).

What is missing are implementation and health-economic studies to define the placement of each therapy under real-world access constraints (2, 9).

1. *Limited epidemiological data:* There is a clear lack of accurate epidemiological data concerning CPG's prevalence, incidence, and stratification by sex, age, and ethnicity. Large-scale national and international epidemiological studies are needed to better understand disease burden and inform healthcare policies.
2. *Lack of objective measures:* There is a standardized protocol for an objective physician assessment of CPG including an IGA for the stage and activity and the PAS (Prurigo Activity and Severity) questionnaire. The patient perspective is still based on subjective assessment of pruritus (WI-NRS) and quality of life. Objective assessment instruments for scratching activity would be highly useful in CPG but are not yet available for clinical routine. Beyond intensity, capturing itch qualities – burning, stinging, crawling – as well as temporal pattern, distribution, and sensory-gain phenomena (alloknesis, hyperknesis) is desirable.
3. *Pathophysiological uncertainty:* Despite recent advances, the precise mechanisms linking immune dysregulation to neuronal sensitization are still unclear. There is a critical need to deepen our understanding of the pathophysiology of CPG:
   - Endotypes: Identification and characterization of CPG endotypes are essential for personalized therapy approaches.
   - Molecular and cytokine interactions: Further studies are needed to elucidate the interactions between key cytokines such as IL-31, IL-4, IL-13, and others involved in CPGN pathogenesis. Understanding the crosstalk between these molecules could provide new therapeutic targets. Also investigating the role of other IL and pathways in large cohorts would be very valuable to understand differences regarding phenotypic expression and different treatments responses.
   - Genetic background and predisposition: There is limited knowledge concerning genetic predisposition factors that may increase susceptibility to CPG. Genetic studies are needed to identify potential markers and underlying mechanisms.
   - Neuroimmune axis: Our understanding of the neuroimmune interaction and its impact on chronic pruritus is still int its initial stages. Investigating the role of neural pathways and neurogenic inflammation is of utmost importance for a deep understanding of CPG.
4. *Comorbidities and their impact:* CPG is frequently associated with systemic comorbidities. Understanding how these conditions influence the disease course and treatment outcomes is important to develop management strategies.
5. *Long-term efficacy and safety of new therapies:* Although dupilumab and nemolizumab have shown promising results in clinical trials, long-term data on their safety and efficacy are still limited. Real-world evidence studies are needed to evaluate sustained responses, potential adverse effects, and the risk of rebound after treatment discontinuation.
6. *Consensus on therapeutic management:* Despite having guidelines for the management of CPG, significant knowledge gaps remain regarding the optimal therapeutic approach for patients with specific underlying conditions, as well as for those who do not adequately respond to current treatments.
7. *Economic impact and healthcare resource utilization:* CPG entails a significant healthcare burden. Real-world data assessing healthcare costs and economic impact are essential and lacking in most countries.
8. *Psychologic burden and need for interdisciplinary care:* CPG severely impact patients' quality of life, causing sleep disturbance, anxiety, depression, and social isolation. Raising awareness of mental health impairment in these patients and including its assessment in all our patients will allow a better and more comprehensive approach to the patients involved.
9. *Efficacy across endotypes:* pivotal CPG trials have not been stratified by biomarker-defined endotype or reported treatment-effect heterogeneity, limiting progress toward precision therapeutics.

Addressing these critical gaps through collaborative international research is essential to enhance patient outcomes in CPG.

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