



# Chronic pruritus of unknown origin (CPUO): Uniform nomenclature and diagnosis as a pathway to standardized understanding and treatment

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Chronic pruritus, defined as itch lasting greater than 6 weeks, is a major unmet clinical problem. In addition to a variety of primary dermatologic conditions, such as atopic dermatitis, psoriasis, and prurigo nodularis, chronic itch results from many unrelated diseases, including chronic kidney disease, hepatobiliary disease, and neuropathic entities such as brachioradial pruritus and notalgia paresthetica. Given the diversity of chronic itch conditions, many attempts have been made to define clinical, diagnostic, and therapeutic guidelines for specific forms of chronic itch.

However, even after exclusion of all known chronic itch disorders, many patients suffer from chronic itch of unknown cause. This has been referred to as chronic idiopathic pruritus (CIP), generalized pruritus of unknown origin (GPUO), and chronic pruritus of unknown origin (CPUO).<sup>1-3</sup> Given the lack of unified terminology and understanding, pathways to investigation and treatment have been limited. We propose uniform nomenclature, diagnostic workup, and classification to help move forward our evolving understanding of this condition.

First, we propose the terminology CPUO to acknowledge our limited understanding of the condition and likelihood that a number of etiologies are likely to be unmasked in the near future. We suggest that the term “generalized” (ie, GPUO) be avoided, because the extent to which this condition is generalized varies. There is also confusion about which conditions fall into this category. In our opinion, if there is well-understood etiology (eg, neuropathic basis of brachioradial pruritus) underlying a specific condition, then CPUO is excluded as a diagnosis. If it is suspected that an etiologic agent (eg,  $\mu$ -opioids) is causing pruritus and patients then improve upon cessation or relapse upon repeat exposure, they would also not have CPUO.

Although we consider CPUO to encompass conditions previously described as “Willan’s itch” or “pruritus of the elderly,” a significant number are not elderly.<sup>4,5</sup> In our opinion, in most cases, pruritus of the elderly is the same condition as CPUO because the etiology remains unknown in both. This is a proposed modification from the British Academy of Dermatology guidelines.<sup>3</sup> It is important to note, and we acknowledge, that the definition of CPUO is

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on advisory boards for Cara Therapeutics, Celgene Corporation, Kiniksa Pharmaceuticals, Menlo Therapeutics, Regeneron Pharmaceuticals, Inc, Sanofi, and Theravance Biopharma. Dr Berger has participated on advisory boards for Menlo Therapeutics, Pfizer, and Sanofi. Dr Yosipovitch has participated on advisory boards for AbbVie, Inc, Bayer, Cerave, Galderma, Kiniksa, Menlo Therapeutics, Ortho, Pfizer, Sanofi Regeneron, Trevi Therapeutics, Novartis, Eli Lilly, and Sienna Biopharmaceuticals.

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**Table I.** Recommended diagnostic workup for chronic pruritus of unknown origin

Presenting symptoms	Pruritus $\geq 6$ weeks with no primary rash
Medical history	Key questions: <ul style="list-style-type: none"> <li>• Timing, location, and duration of pruritus</li> <li>• Medications and comorbidities (eg, narcotic use)</li> <li>• Environment (risk for scabies)</li> </ul>
Physical examination	<ul style="list-style-type: none"> <li>• Complete body skin examination, including genitals (to rule out scabies), looking for primary lesions</li> </ul>
Core laboratory tests (to be performed in all patients)	<ul style="list-style-type: none"> <li>• Complete blood count with differential, liver function tests, renal function tests, thyroid function tests</li> </ul>
Optional laboratory tests (assess as needed based on results of medical history, skin examination, and core laboratory tests)	<ul style="list-style-type: none"> <li>• Skin biopsy is recommended, but not required, in anyone who has a history of a skin lesion in a pruritic site or if suspicion for latent pruritic dermatosis is high based on history or risk factors (eg, dermatitis herpetiformis or bullous pemphigoid in those aged <math>\geq 65</math> years)               <ul style="list-style-type: none"> <li>○ Direct immunofluorescence</li> <li>○ ELISA for bullous pemphigoid</li> </ul> </li> <li>• If malignancy is suspected: refer for malignancy screening (we do not recommend dermatologists workup for malignancy)</li> <li>• If neurologic cause is suspected: refer for neurologic workup (neurology referral is not required for brachioradial pruritus, notalgia paresthetica, and scalp pruritus)</li> </ul>
Diagnosis and treatment	<ul style="list-style-type: none"> <li>• If cause is identified, diagnose and treat accordingly</li> <li>• If no (primary) cause is identified, diagnose as CPUO and continue empiric antipruritic treatments</li> </ul>

CPUO, Chronic pruritus of unknown origin; ELISA, enzyme-linked immunosorbent assay.

likely to become more restricted as etiologies are identified for subsets of conditions currently within this category.

Second, diagnosis of CPUO excludes primary dermatologic or other underlying medical disorders. However, these patients present with some positive findings. These include eosinophilia, mild immunoglobulin E elevation (but  $<1000$  UI/mL), dermal hypersensitivity or spongiotic dermatitis pattern with eosinophils in the dermis on skin biopsy, and small, pink “micropapules” in a generalized distribution. However, we stress that these are not required for the diagnosis of CPUO.

Third, there is a tendency for patients with CPUO to undergo extensive diagnostics. This is because of the concern that practitioners may be missing a serious medical condition (eg, malignancy). However, given a thorough history, examination, and referral, we believe that ancillary testing should be focused within the dermatology clinic. We propose a basic workup strategy as being sufficient to conclude a diagnosis of CPUO (Table I).

In summary:

- We propose the term CPUO to define individuals who present with chronic itch in the absence of an etiology

- CPUO encompasses patients with pruritus of the elderly
- As our understanding of the etiologies of CPUO expands, the scope of this diagnosis will likely become narrower
- We propose a targeted workup for the diagnosis of CPUO
- We emphasize that these recommendations do not supersede an individual clinician’s judgment to order a specific evaluation; index of suspicion should always drive additional diagnostic testing

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