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IFSI-guideline on chronic prurigo including prurigo nodularis

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Abstract

Chronic prurigo (CPG) is a highly burdensome pruritic disease characterized by chronic itch, a prolonged scratching behavior and the development of localized or generalized hyperkeratotic pruriginous lesions. Neuronal sensitization and the development of an itch-scratch cycle contribute to the augmentation of pruritus and the chronicity of the disease. We provide here the first international guideline for a rational diagnostic and therapeutic approach for CPG. Recommendations are based on available evidence and expert opinion. The diagnosis of CPG is made clinically. A detailed medical history together with laboratory and radiological examinations are advised in order to determine the severity of CPG, identify the underlying origin of the itch and assist in the elaboration of a treatment plan. Therapeutically, it is advised to adopt a multimodal approach, including general strategies to control itch, treatment of the underlying pruritic conditions, and of the pruriginous lesions. Topical (corticosteroids, calcineurin inhibitors, capsaicin) and systemic antipruritic agents (eg, gabapentinoids, immunosuppressants, and opioid modulators) as well

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as physical treatment modalities (phototherapy, cryotherapy) should be employed in a step-wise approach. Psychosomatic or psychological interventions may be recommended in CPG patients with signs of psychiatric/psychological comorbidities.

Keywords: Prurigo nodularis, Chronic prurigo, Itch, Guideline, Diagnostic, Treatment

Part I: Introduction

Aims and background

Prurigo nodularis (PN) was described for the first time in the archives of Dermatology at the end of the 19th century. In 1879, William Augustus Hardaway (1850–1923) described PN as *multiple tumors of the skin accompanied by itching* in the *Archives of Dermatology*[1]. The Chicago dermatologist James N. Hyde described it based on his own patients in 1883[2]. The term PN was introduced in 1909 by Hyde and subsequently frequently referred to as PN Hyde. This term was added to the dermatological nomenclature, which already used the term prurigo for heterogeneous conditions. Consistency in the prurigo nomenclature was never achieved due to use of different local terms in different regions without the possibility of modern photographical documentation and scientific exchange. The diversity in nomenclature hindered research and clinical development for a long time. Now, 110 years after introduction of the term prurigo nodularis, we provide the first multinational recommendations for a rational diagnostic and therapeutic approach for this disease.

This guideline is based on expert opinion and on evidence of case series and randomized controlled trials (RCTs). This guideline has limitations due to the low number of available trials, lack of longitudinal cohort studies investigating the course of the disease and best treatment options, lack of a registry with real-world follow-up data regarding healing of the disease and data on adverse events in this population. The recommendations provided here are framed for adult patients, representing the major group of prurigo patients. Children are rarely affected and literature is missing. Many of the experts participating in this guideline have declared conflicts of interest due to their roles in developing new treatments for pruritus.

Methods

The development of this guideline consisted of various stages, including a preparatory survey to assess the state of the art regarding the diagnosis and therapy of chronic prurigo (CPG), a pre-delphi survey and a consensus meeting in which recommendations on diagnostics and therapy were voted upon and an off-line, post-meeting voting, in which experts not present in the consensus meeting voted on the suggested recommendations (**Fig. 1**).

Members of the Task Force Pruritus of the European Academy of Dermatology and Venereology (EADV) worked together in the European Prurigo Project (EPP)[3]. As part of this project, a poll survey aimed to define the state-of-the-art in CPG routine care. The results (Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/ITX/A4) reflected a broad consent among the group and the development of a multinational guideline was decided (in September 2018, during EADV meeting in Paris). Subsequently, itch specialists from the United States were invited to collaborate. The poll survey covered the following topics: medical history taking, questionnaires, dermatological and physical examination, skin biopsies, microbiological tests, microscopic work-up, laboratory and radiologic examinations and involvement of other specialties. In a first stage 29 European experts completed the survey between 16 July 2018 and 27 August 2018, and in a second phase 8 additional experts from the United States filled out the questionnaire between 19 March 2019 and 23 April 2019. The results are shown in Supplementary Table 1 (Supplemental Digital Content 1, http://links.lww.com/ITX/A4).

In a next step, chapters and authors were determined and small groups of experts worked on the literature search and evaluation as well as on framing the recommendations. The proposed

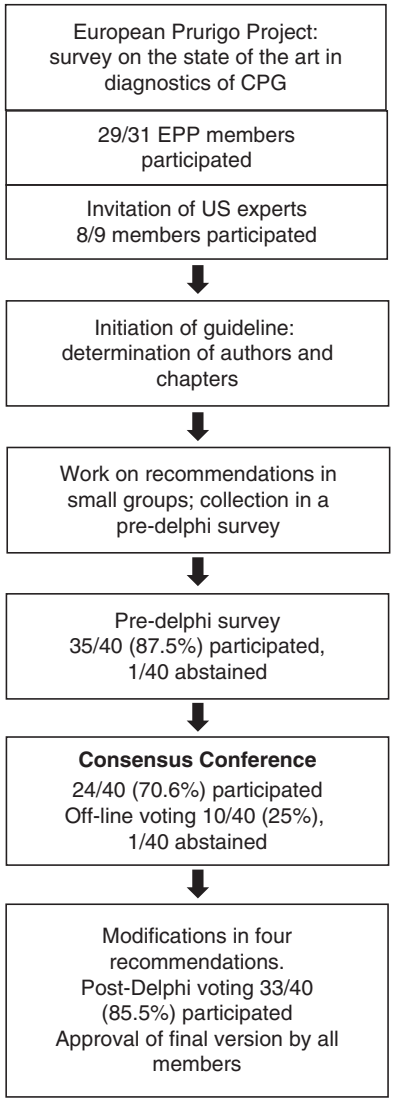

Figure 1. Development of the chronic prurigo guideline. This flowchart summarizes the steps taken for the development of this guideline, in which European and US itch specialists were involved. The first step was to evaluate the state of the art regarding diagnostics of CPG. Afterwards, small groups of specialists worked on the recommendations on diagnostics and therapy of CPG, which were voted on before a consensus conference. The recommendations were further discussed and voted on in the consensus conference and in a postconference online survey. The final step was the approval of this guideline by all participating members. CPG indicates chronic prurigo; EPP, European Prurigo Project.

Table 1

Used wording regarding the level of study quality, recommendations and strength of consensus.

Levels of study quality regarding evidence (GRADE Working Group recommended wording[4])	*High quality*—Further research is very unlikely to change our confidence in the estimate of effect
	Moderate quality—Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
	Low quality—Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
	Very low quality—Any estimate of effect is very uncertain
Levels of recommendations (GRADE Working Group recommended wording[4])	"*We recommend…*"—strong recommendation for the intervention
	"*We suggest…*"—weak recommendation for the intervention
	"*We cannot make a recommendation with respect to…*"—no recommendation
	"*We suggest against…*"—weak recommendation against
	"*We recommend against…*"—strong recommendation against
The strength of consensus was determined by expert voting as follows[4]	*100% consensus*—100% agreement
	Strong consensus—Agreement of > 95% to <100% participants
	Consensus—Agreement of > 75% to 95% participants
	Agreement of the majority —Agreement of > 50% to 75% participants

The GRADE Working Group recommended wording was adopted in this guideline[4].

recommendations were based on available literature and the authors' expert opinion. The evaluation of the references and expert recommendations were made based on the GRADE (Grading of Recommendations Assessement, Development and Evaluation) guidelines (**Table 1**)[4]. All results were collected in a pre-delphi survey. Covered topics included diagnostics (history of CPG, general medical history, clinical assessment, questionnaires, physical examination, laboratory, microbiological and imagological exams, skin biopsy), general therapeutic principles, topical therapies (steroids, calcineurin inhibitors, cryotherapy, capsaicin), phototherapy, systemic therapies (antihistamines, gabapentinoids, immunosuppressants, thalidomide/lenalidomide, opioid modulators, neurokinin-1 receptor antagonists, biologics and small molecules, antidepressants) and psychosomatic therapy. A total of 37 international experts completed the questionnaire between 30 July 2019 and 27 August 2019. The guideline consensus meeting took place on 30 August 2019 in Munich, Germany and was attended by 24 itch experts (**Fig. 1**). Taking the recommendations from the pre-delphi survey as a basis, recommendations on the diagnostic and therapeutic approach of CPG were discussed and voted upon. If consensus on a particular statement could not be reached after the first round of voting, further discussion and voting occurred until a consensus was reached as per the Delphi method (**Table 1**)[5]. Following the consensus conference, eleven members who were not able to participate in the conference had the opportunity to vote on the suggested recommendations from the consensus conference in a postmeeting survey (1 of the members abstained from voting). Additional questions regarding the use of nemolizumab in CPG and regarding referral of CPG patients for psychological, psychosomatic or psychiatric assessment were sent to all participants in a postmeeting survey. The voting results of the conference meeting and postmeeting survey can be consulted in Supplementary Table 2 (Supplemental Digital Content 1, http://links.lww.com/ITX/A4). Consensus could be reached for all topics.

Historical aspects of prurigo

The term prurigo is until today regularly used in dermatology for primary dermatoses and secondary reaction patterns. The term prurigo had already appeared in medical papers in very early history as for example in documents of Aulus Cornelius Celsus (50 BC–50 AD) and was used to describe itchy conditions. Robert Willan (1757–1812) stated in 1798: "I therefore want to use the term prurigo (itching of the skin) for this, an invented word already used by medical writers in the same sense"[2]. Since then, prurigo was classified into various different forms, of which many have strong similarities. There was no clear definition, nor a clinical differentiation, of the various diseases that carry the term prurigo. It even remains unclear for which entity the term has primarily been used and whether it has always been seen in the context of pruritus. The most common and well-known form, PN, was described by J.N. Hyde. This term is still in use today; other terms are now uncommon and, as a result, the conclusion of historical terms on the clinical variant is difficult even today. In 2018, an European initiative (EPP) revised the terminology and suggests to use the term CPG for all clinical subtypes including PN and defined the disease properly for the first time[3].

Epidemiology

Epidemiological data regarding the incidence and prevalence of CPG based on prospective studies are lacking. All age groups can be affected by CPG, even children[6]. Elderly people are most frequently affected[7]. Some observations indicate that African Americans with atopic dermatitis (AD) appear to develop more pruriginous lesions than other racial groups[8,9].

The prevalence of CPG in the United States was recently estimated at 72 per 100,000 individuals aged 18–64 years with health care insurance[10]. Another study found that CPG accounts for an estimated 125,000 ambulatory visits in the United States annually[11].

In an evaluation of emergency department visits in the United States, CPG patients were most likely to be between the ages of 40–59 (50.3% of CPG patients) and 60–79 (31.1% of CPG patients)[12]. Further, a population level study of inpatient hospitalization in the United States found CPG to disproportionately affect minority black, Asian, and Hispanic patients[13].

A recent European study from a German population found a prevalence of 0.1%. Similar to US studies, PN patients tended to be older with a median age at diagnosis of 58.28 years[14].

Definition and terminology

CPG was defined as a distinct disease in 2018 by the Task Force Pruritus of the EADV[3]. The 3 core criteria needed to establish the diagnosis of CPG are (1) the presence of multiple pruriginous lesions (localized or generalized), (2) the presence of chronic

Table 2

Diagnostic criteria for chronic prurigo.

Core Symptoms (Major Criteria)	
Chronic pruritus (≥ 6 wk)	
History and/or signs of repeated scratching (e.g. excoriations and scars)	
Localized or generalized presence of multiple pruriginous lesions*	
*Definition of pruriginous lesion: Excoriated, scaling and/or crusted papules and/or nodules and/or plaques, often with a whitish or pink centre and hyperpigmented border.	
Associated Criteria	
Clinical signs	Pruriginous lesions: usually symmetrically distributed, rarely affect the face and palms
	Signs for scratching: excoriations, scars, lichenification may be present
Range of clinical manifestations	Papular type
	Nodular type
	Plaque type
	Umbilicated type
	Linear type
Symptoms	Usually the pruriginous lesions develop after the beginning of itch
	Quality: itch, burning, stinging or pain
	Signs of chronicity: high intensity of pruritus, alloknesis, hyperknesis, continuous increase in number of lesions
Function	Patients with chronic prurigo may have an impaired quality of life, sleep loss, days of absence from work and/or obsessive-compulsive behavior as a consequence of this disease
Emotions	Possible psychological reactions: depression, anxiety, anger, disgust, shame and helplessness

A summary of major obligatory criteria and associated facultative criteria for the diagnosis of chronic prurigo are presented in this table.
The full range of diagnostic criteria can be consulted at Pereira et al[3].

pruritus (ie, itch lasting longer than 6 wk) and (3) the history and/or sign of a prolonged scratching behavior[3]. Minor criteria are frequently present but are not mandatory to establish the diagnosis of CPG (**Table 2**).

Chronic pruritus (ie, pruritus lasting for ≥ 6 wk) is an obligatory feature of CPG[2]. According to the etiological classification of the International Forum for the Study of Itch (IFSI), chronic pruritus may be of dermatological, systemic, neurological, psychiatric/psychosomatic, multifactorial or unknown origin[15]. Chronic pruritus and the resulting prolonged scratching behavior induce an itch-scratch-cycle as well as neuronal sensitization phenomena, which contribute to the development and perpetuation of CPG[16]. These mechanisms are independent of the origin of the pruritus, since the development of CPG is observed for different underlying etiologies of the pruritus (eg, in AD, nephrogenic pruritus or neurological compression syndromes). As such, CPG may be triggered by different underlying diseases. As many patients are elderly, there may be a lot of independent comorbidities without being a triggering cause of CPG. Therefore, the underlying disease of CPG is not easy to establish and terms such as, for example "pruriginous atopic dermatitis" should be avoided in favor of stating that there are 2 distinct entities, CPG and AD without stating a possibly wrong association.

Pathophysiology

Recent research efforts have led to a better understanding of the cutaneous pathophysiology of CPG. Several cell types including keratinocytes, nerve fibers, vessels, mast cells, inflammatory cells (T-lymphocytes, eosinophils)[17] lead to inflammation, acanthosis, fibrosis, hypervascularization and neuroplasticity. Especially pro-inflammatory Th2 cytokines are involved in CPG lesions[18]. Levels of T-cell–derived interleukin (IL)-31 and its receptor are highly expressed in the skin[19]. The tachykinin substance P (SP), which binds to neurokinin-1 receptors with high affinity, also plays a role in the proinflammatory signaling in CPG and in the release of neurotrophic factors. Dermal SP + -nerves are more frequent in lesional skin of CPG, and may contribute to the development of the disease[20]. In addition, nerve fibers in pruriginous lesions express calcitonin gene related peptide, which contribute to neurogenic inflammation by recruiting inflammatory cells[21]. Immunohistological studies have shown dermal neuronal hyperplasia[22], which is consistent with augmented levels of nerve growth factor and its receptor tyrosine kinase A in the dermis of pruriginous lesions[23]. In the epidermis, the density of the nerve fibers is secondarily diminished[24] owing most likely to axotomy by scratching[25]. The intraepidermal nerve fiber density normalizes after healing of the pruriginous lesions[25]. Despite the neuromorphologic alterations, no functional impairment was detected in peripheral nerves by quantitative sensory testing[26]. Scratching also leads to a barrier defect and promotes the release of proinflammatory mediators. This contributes to the augmentation of itch via activation of itch signaling pathways, a phenomenon termed itch-scratch-cycle[27]. Functional testing could demonstrate neuronal sensitization with increased reaction to peripheral pruritogens and decreased neuronal descending inhibition[28].

Clinical types of CPG

CPG is an umbrella term for a range of clinical manifestations[3]. Pruriginous lesions are defined as skin-colored, pink or red, hyperkeratotic or excoriated, scaling and/or crusted papules and/or nodules and/or plaques. Lesions often show a whitish or pink center and hyperpigmented border lesion[3]. Lesions are symmetrically distributed, however, the number and distribution of lesions may also vary widely from patient to patient (**Fig. 2**).

Depending on the clinical phenotype, 5 subtypes of CPG have been defined (**Table 2**). A distinction is made between CPG papular type (pruriginous papules smaller than 1 cm diameter), nodular type (= prurigo nodularis, pruriginous dome-shaped nodules > 1 cm diameter), plaque type (pruriginous flat plaques > 1 cm, often on the lower leg), umbilicated type (ulcers with pruriginous border) or linear prurigo (linearly arranged pruriginous lesions)[3,29,30]. Of these, the nodular type (prurigo nodularis, syn: chronic nodular prurigo) is the most frequent one. Several subtypes may coexist in 1 patient, usually 1 is predominant, and then eponymous[3].

Burden of CPG

CPG has a significant impact on patients' quality of life as assessed by both dermatological quality of life instruments and general health questionnaire[31]. The impact on quality of life is also reflected by affected sexual life[32]. There is a significant psychological burden of patients with CPG although only cross-sectional studies analyzing this issue have been conducted; therefore the causality is not yet clarified. Patients with CPG have significantly more depression and anxiety and use anxiolytics and antidepressants more often than controls[31,33,34]. Some ethnic

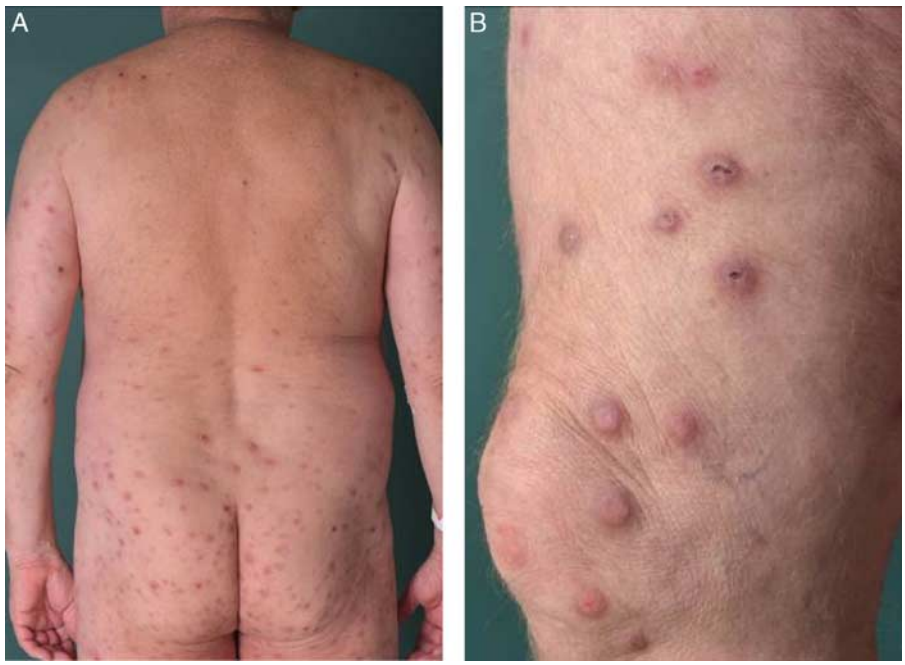

Figure 2. Clinics of chronic prurigo. Overview (A) and detail (B). Notice the positive butterfly sign (A), that is absence of chronic prurigo lesions at the central back caused by the inability to scratch with the hands in this area.

groups like African Americans[8] and also Asians seem more likely to be burdened with CPG and infectious comorbidities[13]. In the United States there is a burden in the health care system for inpatients with CPG: if they are hospitalized, they have longer length of hospital stay and higher cost of care[13].

Part II: Diagnostics

The diagnosis of CPG is made clinically based on the presence of the 3 core criteria. A medical history, clinical, lab and radiologic examination helps to confirm the diagnosis and to determine the severity of CPG, the underlying disease and an individual treatment plan. A recent paper suggests a detailed diagnostic algorithm[35]. Here we summarize the key points of the diagnostics within recommendations. Along the recommendations, that are based on expert opinion, further information is given in **Tables 2–4** and Supplementary Table 1 (Supplemental Digital Content 1, http://links.lww.com/ITX/A4).

History of CPG[36]

Recommendation	Consensus
We recommend taking a history in patients with CPG regarding: duration of CPG and associated itch, localization and clinical state of the skin at the beginning and in the course, associated diseases/intake of drugs, and itch intensity (Table 3).	100% consensus

Clinical state of skin at the beginning of the disease (itch or skin lesions first) is important to differentiate between CPG and skin picking.

General history

Recommendation	Consensus
We recommend taking a general history in patients with CPG considering:	
History of general diseases, eg, kidney disease, liver disease, diabetes, neuropathy	100% consensus
Personal dermatological history, eg, atopic dermatitis, allergies; family history of dermatological diseases	
Current regular medication	
Current symptoms like fatigue, fever, weight loss, sweating at night	

Table 3

CPG related history: key questions.

Question	Agreement (in Percent)
When did CPG begin? (Duration of disease)	100.0
Where did CPG begin? (Initial localization)	94.6
Where is CPG now? (Extent of disease)	86.5
Did the itch begin on normal appearing skin or were skin lesions present when the itch began?	78.4
On average, how intense has the itch been during the past 24 h on a scale from 0 to 10?	81.1
How did the lesions initially look?	73.0
Which general or dermatological disease occurred before or together with the start of prurigo ?	81.1
Have any diseases been newly diagnosed since the start of the prurigo?	78.4
Which previous topical therapies have you used to treat the prurigo?	100.0
Which previous systemic therapies have you used to treat the prurigo?	100.0

Key questions recommended in CPG history taking and the corresponding agreement rate by itch specialists (n = 37, see Supplementary Table 1 for full results, Supplemental Digital Content 1, http://links.lww.com/ITX/A4) is presented in this table.
CPG indicates chronic prurigo.

Table 4

Laboratory analyses.

Lab	Erythrocyte sedimentation rate
	Complete blood count (with differential)
	Ferritin, lactate dehydrogenase
	Kidney retention parameters: creatinine (with estimated GFR), urea
	Liver enzymes: ASAT, ALAT, alkaline phosphate, GGT, bilirubin
	HBV/HCV serology
	Thyroid function test (TSH)
	Fasting glucose or HbA1c
In case of suspect	Total IgE
	HIV
	Indirect and direct immunofluorescence, ELISA BP-180/-230

Laboratory analyses are recommended in the work-up of patients with chronic prurigo in order to identify possible etiological factors underlying the disease and to assist in the development of an individual treatment plan. Recommended laboratory tests are shown for an initial work-up and upon clinical suspicion of atopy, HIV infection or autoimmune skin conditions.

ALAT indicates alanine transaminase; ASAT, aspartate aminotransferase; GFR, glomerular filtration rate; Hba1c, glycated hemoglobin; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodefiecency virus; TSH, thyroid function test.

Clinical assessment

The clinical, dermatological examination aims to distinguish other dermatoses from pruriginous lesions of CPG. Special attention must be paid to the number and distribution of pruriginous lesions in order to document the severity of CPG. The division of pruriginous lesions into the types of CPG is done according to the clinical phenotypes described in clinical types of CPG. The clinical distribution (eg, localized/generalized, symmetrical/asymmetrical) and localization (affected areas) is assessed by standard dermatological documentation. The number of pruriginous lesions can be estimated for documentation. An objective documentation is possible by taking photographs and/or by determining a so-called monitor lesion, usually a pruriginous lesion which is representative of the rest of them.

In order to perform a standardized documentation especially in RCTs, several instruments have been created and validated. The "Prurigo Activity and Severity Score" (PAS) and the "Investigator Global Assessment for Prurigo" (IGA-Prurigo) scale allow not only an objective and standardized documentation but also the determination of the severity of CPG. PAS is a 5-item instrument which includes the documentation of the extent, severity, number, scratch activity and healing of the pruriginous lesions. IGA is a simple rating scale that classifies the presence of pruriginous lesions within 4 stages according to the estimated number of pruriginous lesions.

Recommendation	Consensus
The clinical examination of a patient with CPG involves a thorough inspection of the entire skin including mucous membranes, scalp, nails and anogenital region. Exclude other dermatological conditions.	Strong consensus
Special attention must be paid to the clinical phenotype (clinical types of CPG), the number (affected areas) and distribution (eg, localized/generalized, symmetrical/asymmetrical) of CPG lesions; assessed by standard dermatological documentation	
Presence of the so-called Butterfly sign, ie, no CPG lesions at the central back caused by the inability to scratch with the hands in this area, shall be noted	

Questionnaires

Recommendation	Consensus
We recommend to use regularly itch intensity scales (eg, numerical rating scale) for documentation of the disease and treatment course	100% consensus
In order to help assess the burden and special impact of psychosocial comorbidities of CPG, several patient-reported outcomes (PROs) may be considered to be used for example obtaining the quality-of-life impairment [eg, ItchyQol, Dermatological Life Quality Index (DLQI)], sleep disturbance, or emotional status [eg, Generalized Anxiety Disorder 7 (GAD-7), Patient Health Questionnaire 9 (PHQ-9)]	

Diagnostic approach

Recommendation	Consensus
We suggest performing a symptom-directed general physical examination	Strong consensus
We recommend performing diagnostic laboratory test as presented in Table 4 to establish the initial stage of CPG diagnostics	
We suggest imaging test directed by symptoms and history (expert opinion)	
We suggest that patients with CPG undergo psychological, psychosomatic or psychiatric assessment, if there are clinical signs of compulsory scratching, moderate to severe impairment of life quality, social anxiety or avoidance, depression, anxiety or other psychiatric/psychological comorbidities	

Skin biopsy

Recommendation	Consensus
The diagnosis of CPG can be made in most patients clinically	Consensus
We recommend to perform a biopsy in case of: clinically atypical or refractory CPG; clinical signs or symptoms of dermatological conditions which require a biopsy for their diagnosis	

Part III: Therapy

Currently, no therapy is approved for CPG. Phase II/III trials currently reveal the potency of novel substances in controlling the pruritus of CPG. Accordingly, all recommendations provided here are based on expert recommendations and evidence from RCTs (**Table 5**). It is thus advised to follow a multimodal approach including general strategies to control pruritus, treatment of concomitant, potentially pruritogenic diseases and therapy of pruriginous lesions (**Fig. 3**). As CPG has inflammatory and neuropathic elements, substances such as immunosuppressants and gabapentinoids might be helpful. Despite this, the therapy of CPG remains challenging and of prolonged course.

General principles

Before starting symptomatic topical and/or systemic therapy, CPG patients should undergo a careful diagnostic evaluation, as well as treatment for any underlying disease. It is important to establish an individual therapy regimen for CPG patients. It must consider the age and mobility of the CPG patient, preexisting and concomitant diseases and drug intake. The duration of CPG and the duration and

Table 5

Overview of clinical studies, case series and case reports with anti-pruritic drugs in patients with chronic pruigo.

References	Study Type	Substance	No. Patients	Effect on Itch	Effect on Chronic Prurigo	Quality of Evidence (Table 1)
[37]	CT (left/right comparison)	Betamethasone valerate	12	Higher itch reduction in betamethasone treated side compared with emollient treated side	Most patients (63%) showed a regression of skin lesions	Moderate
[38]	RCT	Betamethasone valerate, calcipotriol	10	Not clear	Reduction in number and size of nodules greater in calcipotriol treated side compared with betamethasone valerate treated side	Moderate
[39]	RCT	1% pimecrolimus cream, 1% hydrocortisone	30	Significant itch reduction with both drugs. No difference between treatments	Significant reduction of scratch with both drugs. No difference between treatments	High
[40]	RCT	Excimer laser, clobetasol propionate	10	Significant itch reduction after treatment with Excimer laser and clobetasol. No difference between treatments	Improvement of nodules in both arms. Higher improvement in Excimer arm compared with clobetasol	Moderate
[41]	CR	Cryotherapy	1	Significant relief	Significant relief	Very low
[42]	CS	Cryosurgery + intralesional steroids + lidocaine	2	Relief	Significant relief	Very low
[43]	OL (uncontrolled)	Capsaicin	33	Significant relief	Significant relief	Moderate
[44]	CS	Capsaicin	7	Substancial relief in 1 patient, relief in 6 patients	Significant relief in 2 patients, relief in 5 patients	Low
[45]	CS/OL	Capsaicin	21	Significant relief	Relief	Moderate
[46]	CS	NB-UVB	10	Significant relief (improvement in all patients)	Significant relief (improvement in all patients)	Moderate
[47]	CS	NB-UVB (after 12 wk thalidomide)	4	Not clear	Significant relief in all patients	Low
[48]	CS	NB-UVB (followed by bath PUVA)	2	Significant relief	Significant relief	Low
[49]	CS	BB-UVB + coal tar + topical corticosteroid	4	Significant relief (complete clearance)	Significant relief	Low
[50]	CS	UVA-1	17	Not clear	Significant relief (impovement in 14/17 patients)	Moderate
[51]	CR	UVA-1 and betamethasone valerate	1	Not clear	Significant relief	Low
[52]	CS	Mostly UVA	19	Not clear	Significant relief (10.5% clear, 42.1% marked improvement, 26.3% slight improvement, 21.1% no response)	Moderate
[53]	CS	UVB, bath-PUVA, oral PUVA	14 (19 treatment courses: UVB 8, bath-PUVA 4, oral PUVA 7)	Not clear	Relief (overall: 84% partial or complete response)	Moderate
[54]	CS	Bath-PUVA (trioxsalen)	15	Not clear	Significant relief (in 13/15 patients)	Moderate
[55]	RCT	8-MOP-Bath-PUVA vs. 8-MOP-Bath-PUVA plus Excimer	22 (11 in each group)	Significant relief	Significant relief in both groups	High
[56]	CS	Excimer laser + topical corticosteroid	2	Significant relief	Significant relief	Low
[57]	CS	Excimer laser	9	Not clear	Significant relief. Complete remission 6/9 (66%), partial remission 3/9 (33%)	Low
[58]	CS	Bilastine (2G antihistamine)	25	Significant relief	Not clear	Low
[59]	CS	Bilastine (2G antihistamine)	24	Significant relief	Not clear	Low
[60]	DBPCS	Dimethypyrindene (1G antihistamine)	11	No effect	Not clear	Low
[61]	CS/OL	Pregabalin	30	Significant relief in 23/30 (76%), relief in 6/30 (20%)	Significant relief in 23/30 (76%), relief in 6/30 (20%) patients	Moderate
[62]	CS	Gabapentin	4	Significant relief	Not clear	Low
[63]	CR	Gabapentin	Not clear	Not clear	Not clear	Very low
[64]	CR	Pregabalin	1	Significant relief	Significant relief	Very low
[65]	CR	Pregabalin	1	Significant relief	Significant relief	Very low
[66]	CS	Pregabalin	7	Significant relief	Significant relief	Low
[67]	CS	Methotrexate	39	Significant relief	Significant relief	Moderate

Table 5

(*Continued*)

References	Study Type	Substance	No. Patients	Effect on Itch	Effect on Chronic Prurigo	Quality of Evidence (Table 1)
[68]	CS	Methotrexate	13	Significant relief	Significant relief	Moderate
[69]	CS	Cyclosporine A	2	Significant relief	Significant relief	Low
[70]	CS	Cyclosporine A	2	Significant relief	Significant relief	Low
[71]	CS	Cyclosporine A	14	Significant relief	Significant relief	Moderate
[72]	CS	Cyclosporine A	8	Significant relief	Significant relief of lesions (6/8 in remission)	Moderate
[73]	CS	Azathioprine	2	Significant relief	Relief	Low
[74]	CS	Thalidomide	6	Significant relief	Significant relief (resolution in 2/6, improvement in 4/6)	Moderate
[75]	CS	Thalidomide	42	Not clear	Relief (remission in 1/42, significant improvement in 5/42, slight to moderate relief in 26/42, no effect in 6/42)	Moderate
[76]	CS	Thalidomide	13	Not clear	Significant relief (complete remission in 7/13, slight improvement in 4/13, no effect in 2/13)	Moderate
[77]	CR	Thalidomide	1	Significant relief	Significant relief	Low
[78]	CR	Thalidomide, Lenalinomide	1	Slow improvement with thalidomide; significant and fast relief with lenalinomide	Significant relief with thalidomide and lenalinomide	Low
[79]	CR	Lenalinomide	1	Significant relief	Significant relief	Low
[80]	CR	Thalidomide, Lenalinomide	1	Relief with thalidomide and lenalinomide	significant with lenalinomide	Very low
[81]	CR	Thalidomide	1	Significant relief	Significant relief	Low
[82]	CS	Naltrexone	17	Relief (complete resolution in 6/17, partial resolution in 7/17, no effect in 4/17)	Relief in responders	Moderate
[83]	CS	Naltrexone	65	Significant relief in 44/65 patients	Relief in 38/65 patients	Moderate
[84]	CR	Butorphanol	1	Relief	Not clear	Very low
[85]	DBPCS	Nalbuphine	62	Relief (the proportion of patients in the nalbuphine meeting 50% responder criteria approached statistical significance ($P = 0.083$))	Not clear	High
[86]	DBPCS	Serlopitant	128	Significant relief	Significant improvement of lesions on the IGA compared to placebo	High
[87]	DBPCS	Aprepitant	58	No effect	No effect	High
[88]	RCT	Aprepitant (topical)	19	No effect	No effect	Moderate
[89]	CS	Aprepitant	13	Significant relief	Not clear	Moderate
[90]	CR	Dupilumab	1	Significant relief	Significant relief	Low
[91]	CS	Dupilumab	4	Significant relief	Not clear	Low
[92]	CS	Dupilumab	3	Significant relief	Relief	Low
[93]	CR	Omalizumab	1	Significant relief	Significant relief	Very low
[94]	CS	Topical ketamine-amitriptyline-lidocaine	18	Significant relief	Not clear	Low
[95]	CR	Mirtazapine	1	Significant relief (especially of nocturnal itch)	Relief	Very low
[96]	CS	Duloxetine	2	Significant relief	Relief	Low
[97]	CS/OL	Amitriptyline	17	Not clear	Not clear	Low
[98]	OL	Paroxetine, fluvoxamine	50	Not clear regarding PN	Relief (complete remission in 14/50, partial remission in 17/50)	Moderate
[99]	CR	Hypnosis and acupuncture combined	1	Significant relief	Significant relief	Very low
[100]	CS	Habit reversal training + plus psychoeducation	6	Not clear	Not clear	Very low
[101]	CS	"Psychiatric intervention"	10	Not clear	Not clear	Very low
[102]	CS	Frontal EMG-Biofeedback combined with systematic desensitization	7	Not clear regarding PN	Not clear	Low

For each study, the number of patients and the effect of the tested substance on itch and chronic prurigo is given when available as well as the quality of evidence as defined on Table 1.
CR indicates case report; CS, case series; CT, controlled trial; DBPCS, double-blind placebo-controlled study; OL, open label study; PN, prurigo nodularis; RCT, randomized controlled trial.

intensity of itch should be considered in treatment planning. The impact on quality of life also affects the choice of treatments. Elderly patients, pregnant or lactating women and children need special attention in treating CPG and itch[103]. The modality of treatment topical, systemic, ultraviolet (UV) phototherapy and combination of any of those] should be discussed with the patient, also to achieve the best possible compliance. CPG patients should be informed about general, especially antipruritic measures including the use of emollients. They can be applied as ointments, creams, lotions and emulsions depending on the status of the skin, especially in consideration of xerosis cutis. Some contain active ingredients such as urea (5%–10%), especially addressing itch[103]. Ingredients like, for example, fragrances and some preservatives may have an allergic or irritant effect and should be avoided. The choice of a topical agent should take into account the eventual presence of erosions, scratch lesions, superinfection, crusts and may include anti-inflammatory and anti-infectious substances. A step-by-step approach should be considered when delineating a therapeutic plan for CPG. Frequently, a combination of topical agents, including moisturizers, systemic drugs, and psychosomatic treatment is needed. As some therapies are not approved for the treatment of CPG, an informed consent and a prescription stating the off-label use of the treatment is required.

Causative therapy

Recommendation	Consensus
Up to 50% of patients suffering from CPG may have an underlying cause and/or have atopic diathesis[27]. Depending on the underlying cause, a specific therapy may be necessary	Strong consensus
No study exists which analyses how successful a causative therapy is concerning healing and long-term control of CPG	
.From clinical experiences, additional symptomatic therapies are necessary due to the chronicity of CPG and possible neuronal sensitization in CPG patients[103,104]	

Emollients

Recommendation	Consensus
We recommend the use of emollients in CPG as supportive care considering the status of the skin including secondary scratch lesions and xerosis cutis (expert opinion)	100% consensus

Topical steroids and calcineurin inhibitors

Recommendation	Consensus
We recommend (moderate to very potent) topical glucocorticosteroids on lesional skin in CPG (based on literature and expert opinion)	
We suggest topical calcineurin inhibitors on lesional skin in CPG (based on literature and expert opinion)	Consensus

The use of topical corticosteroids has to be monitored for side-effects to prevent, for example, skin atrophy upon long-term use.

Cryotherapy, intralesional corticosteroids

Recommendation	Consensus
We suggest cryotherapy and/or intralesional steroids in selected patients with CPG (based on expert opinion)	Consensus

Capsaicin

Recommendation	Consensus
We suggest using topical capsaicin in CPG, especially in localized forms	Consensus

Topical capsaicin should be used in an adequate application frequency, at least 3 ×/d.

UV therapy

Recommendation	Consensus
We recommend UV-therapy (nbUVB (311 nm), UVB broad band, PUVA) in CPG; we suggest excimer laser in selected patients with CPG (based on expert opinion and literature)	Consensus

UV-therapy can be combined with many other therapies (except topical calcineurin inhibitors and substances with photosensitizing effects).

Antihistamines

Antihistamines are still widely used in CPG but evidence of an antipruritic effect is low. Histamine may be one mediator of CPG. Accordingly, the use of antihistamines is justified, but should not be used longer than 4 weeks as monotherapy.

Recommendation	Consensus
We suggest nonsedating and/or sedating H1-antihistamines in CPG (based on literature and expert opinion)	Consensus

Antihistamines: nonsedating antihistamines can be up-dosed.

Gabapentinoids

Recommendation	Consensus
We recommend gabapentinoids (gabapentin, pregabalin) for the treatment of CPG (based on expert opinion and literature)	Consensus

Immunosuppressants

Recommendation	Consensus
We suggest using immunosuppressants such as cyclosporine and methotrexate in CPG	Strong Consensus
We suggest thalidomide only in very exceptional cases of CPG that are refractory to safer therapies by physicians who have experience with the drug (based on expert opinion and literature)	Consensus
We currently cannot make a recommendation with respect to the use of lenalidomide in CPG	

The dosage of the immunosuppressants should be tapered off as soon as possible upon healing of lesions. Further studies to evaluate the efficacy and safety of methotrexate and cyclosporine in CPG are needed. Always consider contraindications, and monitor adverse events and lab values.

Further studies to evaluate the efficacy and safety of lenalidomide in CPG are needed.

Opioid modulators

Endogenous opioid system seems to play a role in the pathogenesis of CPG. Accordingly, there seem to be promising agents

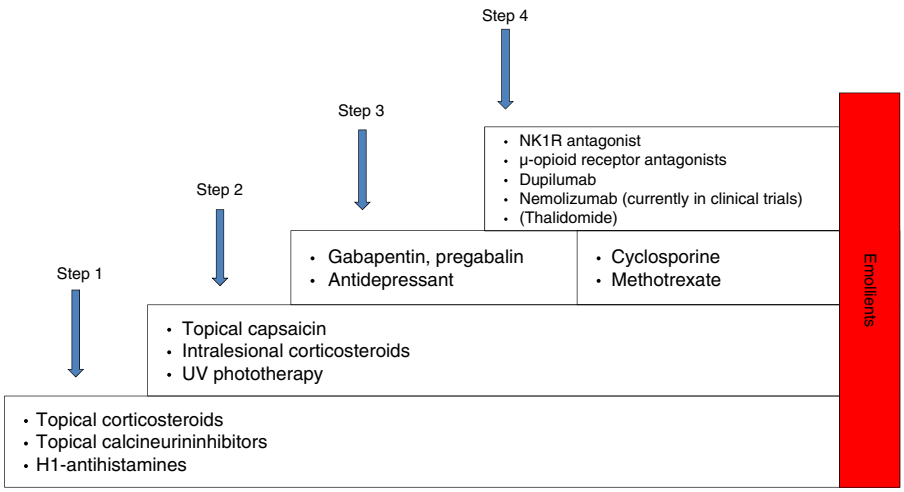

Figure 3. Treatment ladder in chronic prurigo (strong consensus). It is advised to follow a multimodal approach including general strategies to control pruritus, treatment of concomitant, potentially pruritogenic diseases and therapy of pruriginous lesions. Topical and systemic antipruritic agents should be employed in a step-wise approach as detailed by this treatment ladder. Immunosuppressants and gabapentinoids may be chosen according to predominating inflammatory or neuropathic elements of chronic prurigo. The duration of each step is depending on the extent of CPG, the severity of itch, previous treatments and the psychological strain of the CPG patient.

for the treatment of CPG in the near future. However, prospective, randomized, placebo controlled studies are needed to further support their usefulness. Studies are ongoing and final assessments are pending.

Recommendation	Consensus
We suggest the use of mu opioid receptor antagonists in CPG (based on the literature and expert opinion)	100% consensus
We cannot make a recommendation with regard to kappa opioid receptor agonists (based on the literature)	

Neurokinin 1 receptor antagonists

Recommendation	Consensus
We suggest aprepitant in refractory patients with CPG (based on expert opinion)	Consensus

*Regarding Serlopitant: At the time of the consensus conference, a phase II RCT showed itch relief of serlopitant in CPG and our recommendation was: We recommend serlopitant (pending availability) in patients with CPG (based on literature).

Now the results of the phase III RCT have been made public which fail to reach the primary endpoint. We cannot make a recommendation regarding serlopitant in patients with CPG.

Biologics and small molecules

Recommendation	Consensus
We suggest the use of dupilumab in selected patients with CPG (based on literature and expert opinion)	Consensus
We cannot make a recommendation concerning the use of other biologics and small molecules for the therapy in CPG due to lack of evidence (based on the literature)	
We suggest nemolizumab (pending availability) in patients with CPG	Strong consensus

Antidepressants

Recommendation	Consensus
We suggest the use of antidepressants (eg, serotonin reuptake inhibitors, mirtazapine) in patients with CPG (based on expert opinion)	Strong consensus

Mirtazapine is recommended in dosage without antidepressant effects (15 mg).

Psychosomatic therapy

Recommendation	Consensus
We suggest cognitive behavior therapeutic techniques, particularly habit reversal training in combination with itch-modulating techniques, for treatment of CPG (based on literature and expert opinion)	Strong Consensus

More controlled randomized treatment studies are needed in order to investigate the psychological impact on CPG and the impact of CPG on mood, and assess the effects of psychosomatic and psychological interventions in CPG.

Conflict of interest disclosures

S.S. is an investigator for Dermasence, Galderma, Kiniksa Pharmaceuticals, Menlo Therapeutics, Trevi Therapeutics, Novartis, Sanofi, and Vanda Pharmaceuticals Inc.; and is a consultant and/or member of the advisory board for Almirall, Bayer, Beiersdorf, Bellus Health, Bionorica, Cara Therapeutics, Celgene, Clexio Biosciences, DS Biopharma, Galderma, Menlo Therapeutics, Novartis, Perrigo, and Trevi Therapeutics. M.P.P. is an investigator for Trevi Therapeutics; is a consultant for Galderma; and has received speaker honoraria/travel fees from Galderma, Menlo Therapeutics, Novartis and Trevi Therapeutics. T.B. is a consultant for Bellus Health, OptumRx and Sanofi/Regeneron. He is a primary investigator for Kiniksa Pharmaceuticals and Trevi Therapeutics. He is on advisory boards for Menlo Therapeutics and Pfizer Inc. He is on a data monitoring safety board for Ichnos Sciences. C.Z. has received speaker honoraria/travel fees from Beiersdorf and Dermasence. M.A. reports receiving speakers honoraria or grants from, or participated in clinical trials or health services research projects for Abbott/AbbVie, Almirall, Amgen, Biogen Idec, Boehringer Ingelheim, Celgene, Centocor, Eli Lilly, Forward Pharma, Galderma, GSK, Hexal, Janssen, LEO Pharma, Medac, MSD, Novartis, Pfizer, Sandoz, Teva, TK, Trevi, and Xenoport. Svetlana Bobko has received speaker honoraria/travel fees from LEO. E.B. is an investigator for Biogen, Galderma, and is a consultant and/or member of the advisory board for Janssen, Lilly, Celgene, Novartis, Pfizer and received financial support from Sanofi, Abbvie Suephy Chen receives royalties from for-profit companies licensing the ItchyQoL S.C. is an investigator for Incyte and has received research and/or consulting support from companies including Menlo, Abbvie, Janssen, Kiniksa, and Pfizer. ITCH-E, the itch center at Emory, for which Dr S.C. serves at the managing director, has received support from Sanofi, Pfizer, and Genentech. S.B.E. has served as a scientific advisor, advisory board member or consultant to Menlo Therapeutics, New Frontier Bio, Resolute Bio, Sanofi, RAPT Therapeutics, and as an investigator in trials sponsored by Trevi Therapeutics. S.G. has received consulting support from companies including Menlo Therapeutics. Margarida Gonçalo has been a consultant and received speaker honoraria for Novartis and Sanofi Portugal. B.S.K. has served as a consultant for AbbVie, Inc., Cara Therapeutics, Concert Pharmaceuticals, Incyte Corporation, LEO Pharma, Menlo Therapeutics, and Pfizer Inc. He has also participated on the advisory board for Cara Therapeutics, Celgene Corporation, Kiniksa Pharmaceuticals, Menlo Therapeutics, Regeneron Pharmaceuticals Inc., Sanofi Genzyme, and Theravance Biopharma. He is also Founder, Chief Scientific Officer, and stockholder of Nuogen Pharma Inc. He is stockholder of Locus Biosciences. Dr B.S.K has a patent pending for the use of JAK inhibitors for chronic itch. J.L. is investigator for Pfizer, Leo Pharma, Sanofi, Galderma and he received consultancy/ speaker honoraria from Abbvie, Leo Pharma, Galderma, Eli-Lilly, Janssen-Cilag, Roche-Posay, Pierre-Fabre, Novartis, UCB Pharma, Meda Pharma, Mylan, Celgene. F.J.L. is an investigator for DS Biopharma, Eli Lilly, Galderma, Pfizer, Menlo Therapeutics, Trevi Therapeutics and is a member of the advisory boards for Almirall, Celgene, Eli Lilly, Menlo Therapeutics, Novartis, Pfizer, and Trevi Therapeutics. E.A.L. is a member of the scientific Advisory Board of Escient Pharmaceuticals. T.A.L. has been a consultant for Menlo and Novartis. A.L. is a consultant for Galderma and Novartis; and has received speaker honoraria/travel fees from Galderma, Bayer, LEO, Pierre Fabre. 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G.Y. is an investigator for Pfizer, Sun Pharma, Novartis, LEO, Sanofi Regeneron, Kinksa, Trevi, Menlo, Vanda, Cara and is a consultant and or member of advisory Board of Menlo, Trevi, Galderma, GSK, Novartis, Eli Lilly, Bellus, Kinksa, Intercept. The remaining authors declare that they have no financial conflict of interest with regard to the content of this report.

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