

Chronic Prurigo of Nodular Type: A Review

Claudia ZEIDLER¹, Athanasios TSIANAKAS^{1,2}, Manuel PEREIRA¹, Hartmut STÄNDER^{3,4}, Gil YOSIPOVITCH⁵ and Sonja STÄNDER¹
¹Center for Chronic Pruritus, Department of Dermatology, University Hospital Münster, Münster, ²Department of Dermatology, Fachklinik Bad Bentheim, ³Dermatological Practice, Bad Bentheim, ⁴Department of Dermatology, Klinikum Dortmund GmbH, Dortmund, Germany, and ⁵Itch Center Department of Dermatology and Cutaneous Surgery, University of Miami Hospital, Miami, FL, USA

Prurigo nodularis (PN) is a subtype of chronic prurigo presenting single to multiple symmetrically distributed, hyperkeratotic and intensively itching papules and nodules. PN evolves along with chronic pruritus in the context of diverse dermatological, systemic, neurological or psychiatric conditions. Permanent scratching is possibly a major trigger of PN, although its exact pathophysiology remains unclear. Current state-of-the-art therapy for PN consists of topical steroids, capsaicin, calcineurin inhibitors, ultraviolet (UV) therapy, systemic administration of gabapentinoids, μ -opioid receptor antagonists, antidepressants or immunosuppressants. Novel treatment concepts, such as inhibitors of neurokinin-1, opioid and interleukin-31 receptors, have been developed and are currently being clinically tested.

Key words: itch; pruritus; chronic scratch lesions; prurigo nodularis; Hyde's prurigo; interleukin-31; neurokinin-1.

Accepted Aug 23, 2017; Epub ahead of print Aug 23, 2017

Acta Derm Venereol 2018; 98: 173–179.

Corr: Claudia Zeidler, Center for Chronic Pruritus, University Hospital Münster, Von-Esmarch-Str. 58, DE-48149 Münster, Germany. E-mail: claudia.zeidler@ukmuenster.de

P Prurigo nodularis (PN) is a highly pruritic, chronic disease clinically defined by the existence of many, usually symmetrically distributed, hyperkeratotic and erosive papules and nodules (1). PN evolves along with consistent scratching in patients with chronic pruritus, and is a subtype of chronic prurigo (CPG), which was defined recently by members of the European Academy of Dermatology and Venereology (EADV) Task Force Pruritus group, as a skin disease due to neuronal sensitization to itch and development of an itch–scratch cycle (2). The debate on the nature of CPG was initiated over 100 years ago after the first description of PN by Hyde (3), and is ongoing, as relevant aspects of the pathogenesis of CPG remain unclear (4). Part of the confusion is the use of the term “prurigo” for other not-primarily itch-related skin diseases (e.g. actinic prurigo), but also for scratching-related dermatoses. An attempt has been made recently to classify subtypes of CPG based on clinical criteria, differentiating between several types, such as papular, nodular, plaque or umbilicated prurigo, signifying the generally increased acceptance of this terminology (1). An important aspect of this terminology is the acceptance that the presence of CPG should initiate proper treatment and diagnosis of potential underlying di-

seses that might trigger scratching (5). The itch–scratch cycle in CPG appears to be linked to pruritus induced by various disorders, with 50% of PN patients showing an atopic predisposition (6). Other dermatoses, as well as various systemic diseases, infections, neurological and psychiatric disorders, are also known to cause PN (5). Most patients then develop the vicious itch–scratch cycle that is difficult to treat with existing therapies. Itch intensity in PN is thought to be the highest among the different types of chronic itch (5, 7), resulting in reduced quality of life, including sleep disturbances and psychiatric comorbidities (8).

This review summarizes current knowledge and recent findings on the clinical presentation and therapeutic management of PN, discusses ongoing research and indicates areas of future research needs.

EPIDEMIOLOGY

Epidemiological data regarding the incidence and prevalence of PN are lacking. Based on observations from case series, all age groups, including children (9) can be affected by PN, but elderly people are the most frequently affected (5). Furthermore, African Americans with atopic eczema appear to have more PN lesions than other racial groups (10). No conclusion can be drawn on differences between the sexes, as these results have not been reported consistently (5).

PATHOPHYSIOLOGY

Cutaneous inflammation and neuronal plasticity appear to play an important role in PN, but the exact pathogenesis of the condition remains unclear (11).

In 1934, Pautrier (12) observed the presence of neural dermal hyperplasia (Pautrier's neuroma) in PN. Thirty-five years earlier Johnston described hypertrophy of dermal nerve fibres in a papular dermatitis (13).

Histopathological studies revealed increased dermal nerve fibre density and changes in many types of skin cells, including mast cells, collagen fibres, Merkel cells, epidermal keratinocytes, dendritic cells and endothelial cells (14–16). The aforementioned cells cause inflammation and pruritus through the release of tryptase, interleukin-31 (IL-31), prostaglandins, eosinophil cationic protein, histamine, and neuropeptides, such as substance P, calcitonin gene-related peptide (CGRP) and nerve growth factor (NGF) (16–19). In fact, PN skin

biopsies exhibit a 50-fold upregulation of IL-31 mRNA compared with healthy skin biopsies (20). Studies in mouse models showed that the T-cell-derived cytokine IL-31 induces severe pruritus and inflammation (21) by binding to a heterodimeric IL-31 receptor (IL-31 receptor A and oncostatin M receptor subunits) at transient receptor potential cation channels subfamily V or A member 1 (TRPV1+/TRPA1+) C fibres, keratinocytes, macrophages and eosinophils (22). By contrast, the lack of response to antihistamines, indicates that histamine is probably not a major mediator of PN, as it had been considered previously (23). The increased expression of NGF (24) indicates that a substance P-induced signal may contribute to neuronal and dermal hyperplasia (25). Similarly, overexpression of CGRP leads to neurogenic inflammation via the regulation of inflammatory cells, such as eosinophils and mast cells (26).

In contrast to observations in the dermis, hypoplasia of sensory nerves has been reported in the epidermis of PN skin, including interlesional skin, in comparison with healthy skin (16, 27). Moreover, restoration of epidermal nerve fibre density was detected in biopsies of healed nodules (27). A functional study did not detect signs of neuropathy of small fibres in patients with PN (28). Thus, it is likely that the reduced epidermal nerve fibre density is the result of repeated scratching rather than of small fibre neuropathy (27) (Fig. 1).

CLINICAL SIGNS AND SYMPTOMS

PN is characterized by hyperkeratotic, crusted or excoriated, light-red to bright-red papules, nodules or plaques with hyperpigmented borders. Skin lesions may range from a few to hundreds, and their size can range from a

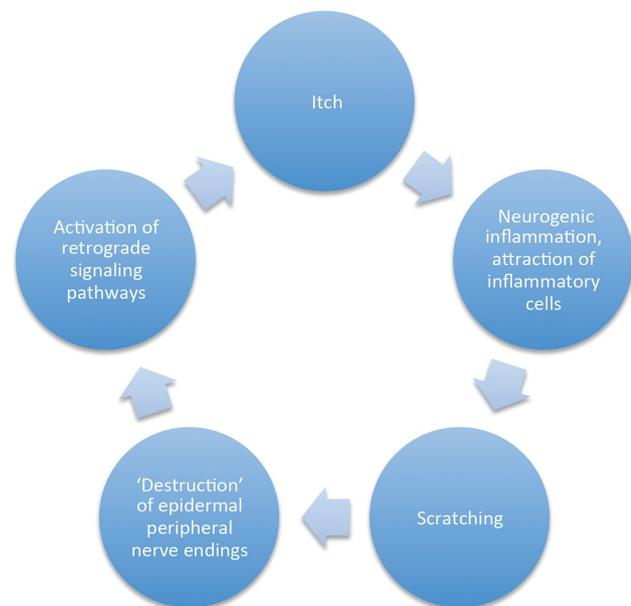


Fig. 1. Itch-scratch cycle and possible pathophysiology of prurigo nodularis.

few millimetres to 2–3 cm. PN can manifest in circumscribed areas, but in most cases is generalized with symmetrical distribution of the lesions on the extensor surfaces of the extremities and the trunk. On the back, the areas that are free of lesions due to the inability of patients to reach them and to scratch, form the so-called “butterfly sign” (Figs 2–4) (1, 11, 29). PN is highly pruritic, with a mean numerical rating scale (0–10) score of 8. Most patients mention more than one quality of pruritic sensation, i.e. a combination of stinging, burning, tingling, heat and cold, independent of the aetiology of PN (5).

In addition to the visible and sensorial symptoms, PN has considerable impact on the quality of life of patients, often leading to sleep disturbance, psychological distress, behavioural/adjustment disorder and social isolation (30, 31).

ASSOCIATED CONDITIONS

Dermatoses

Different inflammatory dermatoses have been observed in association with PN, with atopic eczema being the most frequent (32). These dermatoses evolve with itch and subsequently the itch-scratch cycle promotes PN. Accordingly, PN may coexist with inflammatory der-



Fig. 2. Prurigo nodularis due to atopic predisposition in a 47-year-old woman with typical distribution of lesions including the “butterfly sign” (no lesions on the centre of the back).



Fig. 3. Prurigo nodularis in a 73-year-old patient due to diabetes mellitus.

matoses or continue after their cessation. This association is sometimes described in terms such as “pruriginous atopic eczema”, reflecting the synchronism and biological connection between the conditions. Many patients have PN with an atopic background with no signs of an active dermatosis (Fig. 2).

Although rare, pruritic cutaneous T-cell lymphoma, dermatitis herpetiformis and lichen planus also have the potential to trigger PN (5). In some patients, especially in elderly people, PN lesions may present the initial clinical sign of incipient bullous pemphigoid (33, 34). Therefore, in case of doubt, performing direct immunofluorescence is recommended for diagnosis (35).

Most common systemic and neurological diseases

Many systemic and neurological diseases can result in PN, the most common of which are presented below.

Approximately 18–60% of patients with chronic kidney disease can be affected by chronic itch depending on the region and the definition of itch (36–38). In a study of patients with chronic pruritus due to chronic renal failure, over half of the patients exhibited PN and were those who suffered for longer time from renal failure (39).

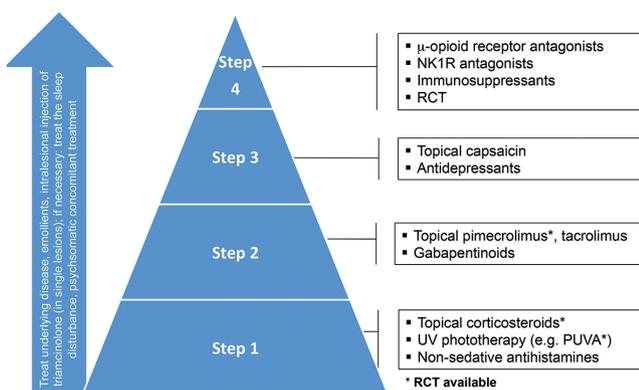


Fig. 4. Prurigo nodularis: treatment algorithm (59). RCT: randomized controlled trial; UV: ultraviolet; PUVA: psoralen plus ultraviolet; NK1R: neurokinin-1 receptor.

According to a representative prospective cross-sectional study in patients attending dialysis units (GEHIS), 10% of hemodialysis patients demonstrated excoriations and scratched nodules with the typical clinical picture of PN (40).

Diabetes mellitus is also associated with PN (Fig. 3) (41). In the case of both, chronic renal failure and diabetes mellitus, PN lesions frequently appear with central ulcerations, resembling Kyrle disease (42, 43). The latter was recently attributed to be a variant of PN (44). Interestingly, chronic pruritus associated with liver disease rarely leads to the formation of PN (45).

Infections, especially HIV, are often associated with PN (46). It is notable that the severity of PN correlates with a lower level of CD4 cells. Areas of high HIV prevalence may also indicate a high prevalence of PN. Following antiretroviral treatments, the symptoms of PN usually improve (47).

Neuropathic diseases can result in localized PN caused by damage to cutaneous or extracutaneous nerves (48). PN can occasionally appear in the context of a post-herpetic neuralgia (49), but also due to other neuropathic forms of chronic pruritus; for example, brachioradial pruritus mostly localized in the dermatome C5/C6 (50).

Psychiatric disorders

Depression and anxiety, as well as tactile hallucinations, can induce psychogenic pruritus and thereby lead to PN (51). This must be distinguished from skin-picking disorder, in which patients manipulate (including scratching) the skin without primarily perceiving pruritus (52). Skin-picking disorder is often correlated with pathological behaviours and/or mental disorders, thus emphasizing the importance of identifying the underlying illness (52).

TREATMENT

Treating PN remains challenging as long as data from randomized controlled trials (RCT) are sparse (**Table I**). An individual treatment plan needs to be established, taking into consideration age, underlying disease, comorbidities, severity of PN, quality of life impairment, and expected side-effects (30). This usually requires a multimodal treatment algorithm, consisting of topical and systemic therapies to address all above-mentioned aspects (Fig. 4) (30). Symptomatic therapy should follow 2 objectives: reduction of itch and complete healing of PN lesions. General measures, for instance the use of an emollient as the basis of therapy, are recommended.

Topical therapy

Topical steroids, pimecrolimus, and calcipotriol are the only topical therapies investigated so far in RCT with PN patients (Table I).

Betamethasone 0.1% cream significantly reduced itch (visual analogue scale (VAS 0–10) before treatment 8.8, VAS after treatment 3.9) in comparison with an antipruritic moisturizing cream (VAS 5.6 after treatment) (Table I), and also resulted in nodule flattening (53). In addition, direct injection of triamcinolone acetonide into the nodules resulted in clinical improvement (54). In inflamed pruriginous lesions, topical steroids can also be combined with an occlusive dressing (55).

Topical calcineurin inhibitors represent a relatively long-term treatment option. Treatment with pimecrolimus led to similar improvement in itch as treatment with hydrocortisone (VAS before 7.1; VAS after pimecrolimus 4.4; $p < 0.001$; VAS after hydrocortisone 4.5; $p < 0.001$) and to distinct amelioration of PN (Table I) (56).

With regard to vitamin D derivatives, calcipotriol ointment significantly decreased the number of PN lesions in comparison with betamethasone valerate (Table I) (57).

Topical capsaicin inhibited pruritus in localized, neuropathic forms of PN and improved the skin condition (58, 59). Another treatment used in the USA, which targets the transient receptor potential channels in the same way as capsaicin, is a combination of topical ketamine and amitriptyline (60).

UV phototherapy

UV phototherapy is a viable therapeutic option, in particular for elderly patients with multi-morbidities and multi-medications. Here, several UV therapies have been reported, such as psoralen plus UVA (PUVA), UVA, and UVB (61–63); in addition, a common and effective option is narrow-band UVB (62).

An accelerated healing process has been observed after combination treatment with a 308-nm excimer laser and PUVA (61). A modified Goeckerman regimen, consisting of daily multi-step broadband UVB therapy followed by the application of crude coal tar and topical steroids under occlusion, was also found to be effective (62). Nevertheless, as the carcinogenic potential of tar is still being discussed, this treatment regimen should be used with caution and only in selected patients (63).

Systemic therapy

Antihistamines. Antihistamines are often used in PN treatment regimens due to the increased numbers of mast cells found in PN lesions. A high-dose non-sedating antihistamine, in combination, if needed, with a sedating antihistamine at night, showed some effect in case series (64). In combination with leukotriene inhibitors, antihistamines decreased the number of PN lesions from between 10 and 290 (mean 107.6) before treatment to between 0 and 154 (mean 42.7) at treatment end (65). However, these were only single reports; the majority of experts agree that antihistamines are not sufficiently ef-

Table I. Treatment of prurigo nodularis based on literature reviews

Drug class – substance	Dosage	Application	Number of patients	Study design	Reference
Antihistamines + leukotriene receptor antagonists – montelukast + fexofenadine	10 mg montelukast/day and 240 mg fexofenadine twice/day	p.o.	12	CS	64
Calcineurin inhibitor – pimecrolimus	1% pimecrolimus cream/day, other half of the body 1% hydrocortisone cream/day	Topical	30	RCT	56
Capsaicin	Capsaicin (0.025% to 0.3%) 4–6 times/day	Topical	33	CS	8
Corticosteroid – betamethasone	Betamethasone vs. moisturizing itch relief cream	Topical	12	RCT	53
Corticosteroid – triamcinolone	7.5–20 mg every 3–4 weeks	Intra-lesional	1	CS	54
Derivative of vitamin D – calcipotriol	50 µg/g calcipotriol ointment once/day, other half of the body: 0.1% betamethasone valerate once/day	Topical	10	RCT	57
Gabapentinoids – gabapentin	300 mg, 3 times/day	p.o.	4	CS	68
Gabapentinoids – pregabalin	75 mg/day	p.o.	30	CS	69
Intravenous immunoglobulins (IVIg)	2 g/kg IVIG for 3 days, once monthly	i.v.	1	CR	82
Immunosuppressants – cyclosporine	3–5 mg/kg cyclosporine/day	p.o.	14	CS	75
Immunosuppressants – lenalidomide	10 mg lenalidomide/day	p.o.	1	CR	80, 81
Immunosuppressants – methotrexate	7.5–20 mg once weekly	s.c.	13	CS	76
Immunosuppressants – thalidomide	Mean 100 mg thalidomide/day	p.o.	42	CS	79
Neurokinin-1 receptor antagonist-aprepitant	80 mg/day	p.o.	13	CS	unpublished data
µ-Opioid receptor antagonist-naltrexone	25–150 mg/day	p.o.	65	CS	71
UV phototherapy – UVB excimer light + bath PUVA	UVB 308-nm excimer light and bath PUVA	UV	22	RCT	61
UV phototherapy + steroid – UVB + LCD + clobetasol	UVB + LCD 5 times weekly plus clobetasol topical occlusive for 4 h	UV, topical	5	CS	62

CS: case series; CR: case report; RCT: randomized controlled trial; p.o.: orally (per os); i.v.: intravenously; s.c.: subcutaneously; PUVA: psoralen plus ultraviolet A; UV: ultraviolet; UVB: ultraviolet B; LCD: coal tar.

fective in PN (30, 66). There is a lack of systematic analyses and RCT of antihistamines in PN.

Gabapentinoids. The addition of gabapentinoids, such as gabapentin and pregabalin, in the treatment scheme of PN should be considered only if other therapies have failed. As proven in RCTs these substances are successfully used in chronic pruritus (67). In PN, improvement has so far been reported only in case series (68, 69). The exact mechanism of action is not yet understood. Stabilization of the spinal nerve membrane by calcium channel blockage, inhibition of glutamate synthesis, or reinforcing of the GABA inhibitory mechanisms so that incoming signals are stopped at the presynaptic membrane, are possible mechanisms (70). When prescribing, the side-effects profile, as well as dosage adjustments for elderly patients and those with renal failure should be taken into account.

Opioid receptor antagonists. Antagonists of the μ -opioid receptor, such as naloxone (intravenous) or naltrexone (oral), demonstrated efficacy in PN (71). An RCT reported significant decrease in itch intensity in cholestatic PN (72). In case series, 67.7% of patients with PN of dermatological origin reported improved symptoms and 38% reported complete healing (71). Despite efficacy, side-effects, such as dizziness and vomiting during the first days of application, must be considered. Combination treatments of κ -opioid receptor agonists with μ -opioid receptor antagonists, such as butorphanol, may also have a beneficial effect on PN (Table I) (73).

Antidepressants. Antidepressants, such as paroxetine, amitriptyline or mirtazapine, showed positive effects in patients with severe PN. In a 2-arm proof of concept study with either paroxetine or fluvoxamine, scratch lesions healed partially or completely in most patients, while the intensity of pruritus decreased significantly (Table I) (74).

Immunosuppressants. After careful consideration of the risk–benefit profile, immunosuppressants can also be considered as a therapeutic option for patients with severe PN. A number of case series described the application of immunosuppressive agents, such as cyclosporine in PN, showing remarkable symptom improvement (75, 76). During immunosuppressant therapy, it is important to monitor blood pressure and laboratory values, especially those of the kidneys. Several cases series describe the use of thalidomide, a neurotoxic and teratogenic drug, for PN (77, 78). A recently published review (79) analysed data from 280 patients with pruritus, mostly due to PN, treated with thalidomide. PN and itch intensity improved in most patients, but the incidence rate of peripheral neuropathy was approximately 20% in the first year of treatment (79). Because of this side-effect thalidomide is commonly a last choice for most severe cases. Lenalidomide, a second-generation thalidomide analogue, decreased pruritus and PN lesions in case re-

ports with conflicting results regarding its neurotoxicity (Table I) (80, 81).

Treatment of PN related to atopic dermatitis, with immunoglobulins in combination with methotrexate, had an antipruritic effect (82).

FUTURE THERAPIES

Based on current understanding of the pathomechanism of PN, targeting the increased levels of IL-31, receptors for substance P and for opioids appear to be promising treatment approaches.

Recent RCTs have investigated the efficacy of the neurokinin-1 receptor antagonists aprepitant (German register: DRKS00005594) and serlopitant (VPD-737; ClinicalTrialGov: NCT02196324) in PN. The latter demonstrated significant itch reduction in the majority of patients with PN (Ständer; unpublished data), as did aprepitant in a previous case series (83).

An RCT, currently running in the US and Europe, is assessing the efficacy of nalbuphine, a dual opioid receptor μ -antagonist/ κ -agonist, in PN (NCT02174419) and appears to be promising. In uraemic pruritus, the use of nalbuphine resulted in a reduction in itch intensity, as demonstrated in an RCT (84).

Future studies in PN will investigate the antipruritic effect of blocking IL-31 at the corresponding receptor. In atopic dermatitis, a similarly itchy disease, the monoclonal antibody nemolizumab has resulted in clinically meaningful improvement in symptom (85, 86).

CONCLUSION

Chronic prurigo, including its subtypes, such as PN, is an itch–scratch cycle related disease based on neuronal sensitization processes. As long as the pathophysiology of PN is not completely clear, its management will represent a therapeutic challenge. It is hoped that the multiple ongoing RCTs on novel targets, such as IL-31, neurokinin-1 and opioid receptors, will lead to effective treatments for this intractable disease with persistent, chronic itch.

ACKNOWLEDGEMENTS

The authors would like to thank the German Federal Ministry of Education and Research (BMBF; No. 01KG1305 to AT and SST) and the European Academy for Dermatology and Venereology (EADV, No. 2016-012 to MP) for their support for this work, Galderma International financial support for this publication, and Helena Karajiannis for assistance in preparation of the manuscript.

Conflicts of interest. SS received advisory honoraria from Almirall, Beiersdorf, Chugai Pharma, Creabilis, Daiichi Sankyo, Galderma, Helsinn, Kneipp, Maruho, Merz, Nerre, Trevi, Vanda, Menlo, Ziarco. GY received honoraria as consultant for advisory board work and as investigator from Trevi, Opko, Menlo, Creabilis, Chugai Pharma, Pfizer, Eli Lilly, Celgene, Anacor, Tioga, Roche, GSK, J&J, and LEO Foundation.

REFERENCES

- Schedel F, Schurmann C, Metze D, Ständer S. Prurigo. Klinische Definition und Klassifikation. *Hautarzt* 2014; 65: 684–690.
- Ständer S. Prurigo nodularis. 2017 [cited 2017 June 2]. Available from: <http://www.pruritus-symposium.de/specialistinformation.html>.
- Hyde JN. A practical treatise on disease of the skin for the use of students and practitioners. 1st edn. Philadelphia: Henry C. Lea's Son & Co., 1883.
- Ständer S, Mettang T. Prurigo nodularis. Ein Rätsel seit mehr als 100 Jahren. *Hautarzt* 2014; 65: 672–673.
- Iking A, Grundmann S, Chatzigeorgakidis E, Phan NQ, Klein D, Ständer S. Prurigo as a symptom of atopic and non-atopic diseases: aetiological survey in a consecutive cohort of 108 patients. *J Eur Acad Dermatol Venereol* 2013; 27: 550–557.
- Tanaka M, Aiba S, Matsumura N, Aoyama H, Tagami H. Prurigo nodularis consists of two distinct forms: early-onset atopic and late-onset non-atopic. *Dermatology* 1995; 190: 269–276.
- Mollanazar NK, Sethi M, Rodriguez RV, Nattkemper LA, Ramsey FV, Zhao H, et al. Retrospective analysis of data from an itch center: integrating validated tools in the electronic health record. *J Am Acad Dermatol* 2016; 75: 842–844.
- Schneider G, Driesch G, Heuft G, Evers S, Luger TA, Ständer S. Psychosomatic cofactors and psychiatric comorbidity in patients with chronic itch. *Clin Exp Dermatol* 2006; 31: 762–767.
- Amer A, Fischer H. Prurigo nodularis in a 9-year-old girl. *Clin Pediatr (Phila)* 2009; 48: 93–95.
- Vachiramam V, Tey HL, Thompson AE, Yosipovitch G. Atopic dermatitis in African American children: addressing unmet needs of a common disease. *Pediatr Dermatol* 2012; 29: 395–402.
- Vaidya DC, Schwartz RA. Prurigo nodularis: a benign dermatosis derived from a persistent pruritus. *Acta Dermatovenerol Croat* 2008; 16: 38–44.
- Pautrier LM. Le neurone de la lichenification circonscrite nodulaire chronique (lichen ruber obtusus corne prurigo nodularis). *Ann Dermatol Syph* 1934: 897.
- Johnston JC. A papular persistent dermatitis: report of an undescribed disease. *J Cutan Dis* 1899: 49.
- Weigelt N, Metze D, Ständer S. Prurigo nodularis: systematic analysis of 58 histological criteria in 136 patients. *J Cutan Pathol* 2010; 37: 578–586.
- Raap U, Ikoma A, Kapp A. Neurophysiologie des Pruritus. *Hautarzt* 2006; 57: 379–380, 382–374.
- Schuhknecht B, Marziniak M, Wissel A, Phan NQ, Pappai D, Dangelmaier J, et al. Reduced intraepidermal nerve fibre density in lesional and nonlesional prurigo nodularis skin as a potential sign of subclinical cutaneous neuropathy. *Br J Dermatol* 2011; 165: 85–91.
- Groneberg DA, Serowka F, Peckenschneider N, Artuc M, Grutzkau A, Fischer A, et al. Gene expression and regulation of nerve growth factor in atopic dermatitis mast cells and the human mast cell line-1. *J Neuroimmunol* 2005; 161: 87–92.
- Johansson O, Liang Y, Emtestam L. Increased nerve growth factor- and tyrosine kinase A-like immunoreactivities in prurigo nodularis skin – an exploration of the cause of neurohyperplasia. *Arch Dermatol Res* 2002; 293: 614–619.
- Liang Y, Marcusson JA, Jacobi HH, Haak-Frendscho M, Johansson O. Histamine-containing mast cells and their relationship to NGF-immunoreactive nerves in prurigo nodularis: a reappraisal. *J Cutan Pathol* 1998; 25: 189–198.
- Sonkoly E, Muller A, Lauerma AI, Pivarcsi A, Soto H, Kemeny L, et al. IL-31: a new link between T cells and pruritus in atopic skin inflammation. *J Allergy Clin Immunology* 2006; 117: 411–417.
- Arai I, Tsuji M, Takeda H, Akiyama N, Saito S. A single dose of interleukin-31 (IL-31) causes continuous itch-associated scratching behaviour in mice. *Exp Dermatol* 2013; 22: 669–671.
- Raap U, Wichmann K, Bruder M, Ständer S, Wedi B, Kapp A, et al. Correlation of IL-31 serum levels with severity of atopic dermatitis. *J Allergy Clin Immunology* 2008; 122: 421–423.
- Murota H, Kitaba S, Tani M, Wataya-Kaneda M, Azukizawa H, Tanemura A, et al. Impact of sedative and non-sedative antihistamines on the impaired productivity and quality of life in patients with pruritic skin diseases. *Allergol Int* 2010; 59: 345–354.
- Haas S, Capellino S, Phan NQ, Bohm M, Luger TA, Straub RH, et al. Low density of sympathetic nerve fibers relative to substance P-positive nerve fibers in lesional skin of chronic pruritus and prurigo nodularis. *J Dermatol Sci* 2010; 58: 193–197.
- Matsumura S, Terao M, Murota H, Katayama I. Th2 cytokines enhance TrkA expression, upregulate proliferation, and downregulate differentiation of keratinocytes. *J Dermatol Sci* 2015; 78: 215–223.
- Liang Y, Jacobi HH, Reimert CM, Haak-Frendscho M, Marcusson JA, Johansson O. CGRP-immunoreactive nerves in prurigo nodularis – an exploration of neurogenic inflammation. *J Cutan Pathol* 2000; 27: 359–366.
- Bobko S, Zeidler C, Osada N, Riepe C, Pfliederer B, Pogatzki-Zahn E, et al. Intraepidermal nerve fibre density is decreased in lesional and inter-lesional prurigo nodularis and reconstitutes on healing of lesions. *Acta Derm Venereol* 2016; 96: 404–406.
- Pereira MP, Pogatzki-Zahn E, Snels C, Vu T, Uceyler N, Loser K, et al. There is no functional small-fiber neuropathy in prurigo nodularis despite neuroanatomical alterations. *Exp Dermatol* 2017; 26: 969–971.
- Schedel F, Schürmann C, Augustin M, Metze D, Blome C, Zeidler C, and Ständer S. Prurigo nodularis: introduction of a re-defined classification and prurigo activity score (PAS). *Acta Derm Venereol* 2013; 93: 610.
- Weisshaar E, Szepietowski JC, Darsow U, Misery L, Wallengren J, Mettang T, et al. European guideline on chronic pruritus. *Acta Derm Venereol* 2012; 92: 563–581.
- Tessari G, Dalle Vedove C, Loschiavo C, Tessitore N, Rugiu C, Lupo A, et al. The impact of pruritus on the quality of life of patients undergoing dialysis: a single centre cohort study. *J Nephrol* 2009; 22: 241–248.
- Pugliarello S, Cozzi A, Gisondi P, Girolomoni G. Phenotypes of atopic dermatitis. *J Dtsch Dermatol Ges* 2011; 9: 12–20.
- Al-Salhi W, Alharithy R. Pemphigoid nodularis. *J Cutan Med Surg* 2015; 19: 153–155.
- Cliff S, Holden CA. Pemphigoid nodularis: a report of three cases and review of the literature. *Br J Dermatol* 1997; 136: 398–401.
- Feliciani C, Joly P, Jonkman MF, Zambruno G, Zillikens D, Ioannides D, et al. Management of bullous pemphigoid: the European Dermatology Forum consensus in collaboration with the European Academy of Dermatology and Venereology. *Br J Dermatol* 2015; 172: 867–877.
- Weiss M, Mettang T, Tschulena U, Passlick-Deetjen J, Weisshaar E. Prevalence of chronic itch and associated factors in haemodialysis patients: a representative cross-sectional study. *Acta Derm Venereol* 2015; 95: 816–821.
- Solak B, Acikgoz SB, Sipahi S, Erdem T. Epidemiology and determinants of pruritus in pre-dialysis chronic kidney disease patients. *Int Urol Nephrol* 2016; 48: 585–591.
- Ramakrishnan K, Bond TC, Claxton A, Sood VC, Kootsikis M, Agnese, et al. Clinical characteristics and outcomes of end-stage renal disease patients with self-reported pruritus symptoms. *Int J Nephrol Renovasc Dis* 2013; 7: 1–12.
- Bohme T, Heitkemper T, Mettang T, Phan NQ, Ständer S. Klinische Charakteristika und Prurigo nodularis bei nephrogenem Pruritus. *Hautarzt* 2014; 65: 714–720.
- Hayani K, Weiss M, Weisshaar E. Clinical findings and provision of care in haemodialysis patients with chronic itch: new results from the German Epidemiological Haemodialysis Itch Study. *Acta Derm Venereol* 2016; 96: 361–366.
- Tseng HW, Ger LP, Liang CK, Liou HH, Lam HC. High prevalence of cutaneous manifestations in the elderly with diabetes mellitus: an institution-based cross-sectional study in Taiwan. *J Eur Acad Dermatol Venereol* 2015; 29: 1631–1635.
- White CR, Jr., Heskell NS, Pokorny DJ. Perforating folliculitis of hemodialysis. *Am J Dermatopathol* 1982; 4: 109–116.

43. Hurwitz RM, Melton ME, Creech FT, 3rd, Weiss J, Handt A. Perforating folliculitis in association with hemodialysis. *Am J Dermatopathol* 1982; 4: 101–108.
44. Kestner RI, Ständer S, Osada N, Ziegler D, Metze D. Acquired reactive perforating dermatosis is a variant of prurigo nodularis. *Acta Derm Venereol* 2017; 97: 249–254.
45. Mettang T, Vonend A, Raap U. Prurigo nodularis bei Dermatosen und systemischen Erkrankungen. *Hautarzt* 2014; 65: 697–703.
46. Magand F, Nacher M, Cazorla C, Cambazard F, Marie DS, Couppie P. Predictive values of prurigo nodularis and herpes zoster for HIV infection and immunosuppression requiring HAART in French Guiana. *Trans R Soc Trop Med Hyg* 2011; 105: 401–404.
47. Ouattara I, Eholie SP, Aoussi E, Bissagnene E, Raffi F. Prurigo chez le patient infecté par le VIH : le traitement antirétroviral peut-il l'éradiquer? *Med Mal Infect* 2009; 39: 415–416.
48. Stumpf A, Ständer S. Neuropathic itch: diagnosis and management. *Dermatol Ther* 2013; 26: 104–109.
49. De D, Dogra S, Kanwar AJ. Prurigo nodularis in healed herpes zoster scar: an isotopic response. *J Eur Acad Dermatol Venereol* 2007; 21: 711–712.
50. Mirzoyev SA, Davis MD. Brachioradial pruritus: Mayo Clinic experience over the past decade. *Br J Dermatol* 2013; 169: 1007–1015.
51. Ständer S, Weisshaar E, Mettang T, Szepletowski JC, Carstens E, Ikoma A, et al. Clinical classification of itch: a position paper of the International Forum for the Study of Itch. *Acta Derm Venereol* 2007; 87: 291–294.
52. Gieler U, Consoli SG, Tomas-Aragones L, Linder DM, Jemec GB, Poot F, et al. Self-inflicted lesions in dermatology: terminology and classification – a position paper from the European Society for Dermatology and Psychiatry (ESDaP). *Acta Derm Venereol* 2013; 93: 4–12.
53. Saraceno R, Chiricozzi A, Nistico SP, Tiberti S, Chimenti S. An occlusive dressing containing betamethasone valerate 0.1% for the treatment of prurigo nodularis. *J Dermatolog Treat* 2010; 21: 363–366.
54. Richards RN. Update on intralesional steroid: focus on dermatoses. *J Cutan Med Surg* 2010; 14: 19–23.
55. Wallengren J. Prurigo: diagnosis and management. *Am J Clin Dermatol* 2004; 5: 85–95.
56. Siepmann D, Lotts T, Blome C, Braeutigam M, Phan NQ, Butterfass-Bahloul T, et al. Evaluation of the antipruritic effects of topical pimecrolimus in non-atopic prurigo nodularis: results of a randomized, hydrocortisone-controlled, double-blind phase II trial. *Dermatology* 2013; 227: 353–360.
57. Wong SS, Goh CL. Double-blind, right/left comparison of calcipotriol ointment and betamethasone ointment in the treatment of prurigo nodularis. *Arch Dermatol* 2000; 136: 807–808.
58. Ständer S, Luger T, Metze D. Treatment of prurigo nodularis with topical capsaicin. *J Am Acad Dermatol* 2001; 44: 471–478.
59. Ständer S, Moormann C, Schumacher M, Buddenkotte J, Artuc M, Shpacovitch V, et al. Expression of vanilloid receptor subtype 1 in cutaneous sensory nerve fibers, mast cells, and epithelial cells of appendage structures. *Exp Dermatol* 2004; 13: 129–139.
60. Griffin JR, Davis MD. Amitriptyline/Ketamine as therapy for neuropathic pruritus and pain secondary to herpes zoster. *J Drugs Dermatol* 2015; 14: 115–118.
61. Hammes S, Hermann J, Roos S, Ockenfels HM. UVB 308-nm excimer light and bath PUVA: combination therapy is very effective in the treatment of prurigo nodularis. *J Eur Acad Dermatol Venereol* 2011; 25: 799–803.
62. Sorenson E, Levin E, Koo J, Berger TG. Successful use of a modified Goeckerman regimen in the treatment of generalized prurigo nodularis. *J Am Acad Dermatol* 2015; 72: e40–42.
63. Paghdal KV, Schwartz RA. Topical tar: back to the future. *J Eur Acad Dermatol Venereol* 2009; 61: 294–302.
64. Schulz S, Metz M, Siepmann D, Luger TA, Maurer M, Ständer S. Antipruritic Wirksamkeit einer hoch dosierten Antihistaminikatherapie. *Hautarzt* 2009; 60: 564–568.
65. Shintani T, Ohata C, Koga H, Ohyama B, Hamada T, Nakama T, et al. Combination therapy of fexofenadine and montelukast is effective in prurigo nodularis and pemphigoid nodularis. *Dermatol Ther* 2014; 27: 135–139.
66. Fostini AC, Girolomoni G, Tessari G. Prurigo nodularis: an update on etiopathogenesis and therapy. *J Dermatolog Treat* 2013; 24: 458–462.
67. Gunal AI, Ozalp G, Yoldas TK, Gunal SY, Kirciman E, Celiker H. Gabapentin therapy for pruritus in haemodialysis patients: a randomized, placebo-controlled, double-blind trial. *Nephrol Dial Transplant* 2004; 19: 3137–3139.
68. Gencoglan G, Inanir I, Gunduz K. Therapeutic hotline: treatment of prurigo nodularis and lichen simplex chronicus with gabapentin. *Dermatol Ther* 2010; 23: 194–198.
69. Mazza M, Guerriero G, Marano G, Janiri L, Bria P, Mazza S. Treatment of prurigo nodularis with pregabalin. *J Clin Pharm Ther* 2013; 38: 16–18.
70. Scheinfeld N. The role of gabapentin in treating diseases with cutaneous manifestations and pain. *Int J Dermatol* 2003; 42: 491–495.
71. Phan NQ, Lotts T, Antal A, Bernhard JD, Ständer S. Systemic kappa opioid receptor agonists in the treatment of chronic pruritus: a literature review. *Acta Derm Venereol* 2012; 92: 555–560.
72. Bergasa NV. The pruritus of cholestasis: facts. *Hepatology* 2015; 61: 2114.
73. Dawn AG, Yosipovitch G. Butorphanol for treatment of intractable pruritus. *J Am Acad Dermatol* 2006; 54: 527–531.
74. Ständer S, Bockenholt B, Schurmeyer-Horst F, Weishaupt C, Heuft G, Luger TA, et al. Treatment of chronic pruritus with the selective serotonin re-uptake inhibitors paroxetine and fluvoxamine: results of an open-labelled, two-arm proof-of-concept study. *Acta Derm Venereol* 2009; 89: 45–51.
75. Siepmann D, Luger TA, Ständer S. Antipruritic effect of cyclosporine microemulsion in prurigo nodularis: results of a case series. *J Dtsch Dermatol Ges* 2008; 6: 941–946.
76. Spring P, Gschwind I, Gilliet M. Prurigo nodularis: retrospective study of 13 cases managed with methotrexate. *Clin Exp Dermatol* 2014; 39: 468–473.
77. Andersen TP, Fogh K. Thalidomide in 42 patients with prurigo nodularis Hyde. *Dermatology* 2011; 223: 107–112.
78. Taefehnorooz H, Truchetet F, Barbaud A, Schmutz JL, Bursztejn AC. Efficacy of thalidomide in the treatment of prurigo nodularis. *Acta Derm Venereol* 2011; 91: 344–345.
79. Sharma D, Kwatra SG. Thalidomide for the treatment of chronic refractory pruritus. *J Am Acad Dermatol* 2016; 74: 363–369.
80. Liu H, Gaspari AA, Schleichert R. Use of lenalidomide in treating refractory prurigo nodularis. *J Drugs Dermatol* 2013; 12: 360–361.
81. Kanavy H, Bahner J, Korman NJ. Treatment of refractory prurigo nodularis with lenalidomide. *Arch Dermatol* 2012; 148: 794–796.
82. Feldmeyer L, Werner S, Kamarashev J, French LE, Hofbauer GF. Atopic prurigo nodularis responds to intravenous immunoglobulins. *Br J Dermatol* 2012; 166: 461–462.
83. Ständer S, Siepmann D, Herrgott I, Sunderkotter C, Luger TA. Targeting the neurokinin receptor 1 with aprepitant: a novel antipruritic strategy. *PLoS One* 2010; 5: e10968.
84. Hawi A, Alcorn H, Jr, Berg J, Hines C, Hait H, Sciascia T. Pharmacokinetics of nalbuphine hydrochloride extended release tablets in hemodialysis patients with exploratory effect on pruritus. *BMC Nephrol* 2015; 16: 47.
85. Ruzicka T, Hanifin JM, Furue M, Pulka G, Mlynarczyk I, Woltenberg A, et al. Anti-interleukin-31 receptor A antibody for atopic dermatitis. *N Engl J Med* 2017; 376: 826–835.
86. Schneider LC. ditching the itch with anti-type 2 cytokine therapies for atopic Dermatitis. *N Engl J Med* 2017; 376: 878–879.