Current Concepts of Pathophysiology, Epidemiology and Classification of Pruritus

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SUMMARY
Discovery of pruritus-specific mediators and receptors facilitated the neurobiological concept of pruritus: itch-specific (histamine-dependent and histamine-independent C-fibers); itch-specific receptors on cutaneous and spinal neurons; “dialogue” between the pruritus-specific neurons and cells in the skin; peripheral and central mediation of pruritus; functional “pruritus-specific matrix” in the brain with a role of pruritus center. In 10%–50% of persons without skin diseases, pruritus is considered the manifestation of a systemic disorder. Identification of pruritus within autoimmune and inflammatory diseases in dermatology is based on the clinical picture and nature of the underlying disease, implying the development of pruritus on primarily and/or secondarily inflamed skin. In the internal medicine, pruritus commonly presents on primarily non-inflamed skin., involvement of the skin and gastrointestinal tract are two independent risk factors of pruritus in systemic sclerosis, and of anal/vulvar pruritus. Classification combines etiological and clinical criteria and should be considered the only segment of a comprehensive approach to pruritus of unknown origin.

Keywords: pruritus; skin diseases; prevalence; comorbidity

INTRODUCTION
As Liddell [1] wrote in his paper, pruritus vulvae, senile pruritus and prurigo were described by Hippocrates of Cos (460-377 BC). In 1660, a German physician Samuel Hafenreffer [2] was the first to define pruritus (s. itch; kinesis) as a sensation that may provoke scratching. Nowadays, pruritus is considered a sensation that, if sufficiently strong, provokes reflex/conscious scratching or desire to scratch [3]. Previously, pruritus was considered a mild pain. Both sensations share common features: receptors in the form of unmyelinated sensory nerve endings (C-fibers) with axons entering the dorsal horn of the spinal cord; secondary transmission neurons that ascend within the contralateral spinothalamic tract. However, pruritus cannot be transformed to pain and stimulation of fascicles that results in pain cannot evoke pruritus, thus two distinct sensations probably interact [4].

If peripheral, itch and pain are induced by activation of receptors, namely, free unmyelinated sensory nerve endings (C-fibers) in the epidermis and epithelia. These fibers are anatomically identical, but functionally distinct. It was believed that itch occurred after stimulation of non-specialized free unmyelinated nerve endings [5]. However, Schmelz et al. [6] demonstrated a small subset (5%) of itch-specific histamine-sensitive slow conducting unmyelinated C-fibers, which only transmit itch (and temperature) but not pain. These are: mechano-insensitive and termed CMi-fibers; selectively activated demonstrating spontaneous activity in chronic pruritic dermatoses. However, mechano- and heat-sensitive C-fibers (CMH), called polymodal nociceptors, are histamine-insensitive and transmit pain. Identification of the second-order neurons, an itch-specific subclass of lamina I spinothalamic tract neurons, has demonstrated that specific neurons also transmit itch centrally [5, 6, 7].

PATHOPHYSIOLOGY
Different C-fibers are involved in pruritus. There are sensory nerve fibers, present both in peripheral and ascending sensory neurons in the spinal cord and thalamus that are histamine-insensitive but transmit itch, mechanical stimuli and pain. Moreover, the presence of the heat-sensitive receptor TRPV1 (transient receptor potential vanilloid ion channel-1) on the CMi-fibers is needed in histamine-mediated pruritus. These receptors are also expressed on keratinocytes, dendritic and mast cells, and are important for pruritus in the inflammatory skin conditions [8-11].

In the skin, different sensory receptors also exist on resident/temporary present cells. The epidermis itself, particularly keratinocytes, constitute the “itch receptor”. Only histamine receptors were previously incorrectly associated with pruritus, since the pain can be evoked by histamine and patients can have pain and itch at the same site [12, 13]. TRPV1, termed the capsaicin receptor, because it can be activated by topical capsaicin, mediates pain and itch. TRPV1 is present on CMi and CMH C-fibers and many cells including keratinocytes. When activated, burning pain occurs initially. In continuous activation of C-fibers, capsaicin...
Histamine plays primary pruritic role in urticaria and mastocytosis, via histamine receptors 1 and 4 (H1, H4). In the skin, H1 is expressed on sensory nerves and endothelia, H4 on Th2 cells, mast cells, fibroblasts, keratinocytes and hematopoietic cells. When H4 is activated on Th2 cells, these cells produce pruritic IL-31. This production is enhanced by the Staphylococcus aureus superantigens. In the skin, receptor for IL-31 is expressed on sensory C-fibers, keratinocytes, and dorsal spinal ganglia. In atopic dermatitis, IL-31 in the peripheral blood and skin is elevated and correlates with the severity of disease. Elevated IL-31 in the peripheral blood was demonstrated in the chronic spontaneous urticaria [14, 15].

Among the external/environmental pruritogens, only chloroquine, opioids and plant cysteine proteases have their own receptors on sensory neurons. The protease-activated receptor (PAR) family comprises G protein-coupled receptors (GPCRs), found on primary sensory neurons and dorsal root ganglia (DRG) neurons. Activated PARs can sensitize TRPV1. Initially, PARs were linked to inflammation: the elevated expression was detected in the lesional skin in atopic dermatitis. During inflammation, there is a cross-talk between dermal mast cells and C-fibers: mast cell-derived tryptase activates PAR2 on neuron terminals triggering secretion/release of CGRP and SP, which bind to the CGRP-receptor (CGRPr) and neurokinin-1 receptor (NKR1), respectively. Neurokinin receptors 1 to 3 are expressed on keratinocytes, endothelium, mast cells and spinal dorsal horn neurons. If it binds to NKR1 on mast cells, SP activates (degranulates) them. In the therapy of individual patients with the renal failure, suppression of pruritus. Thus, antagonists of the µ-opioid receptors (naloxone, naltrexone, nalmefene), are effective in cholestasis, chronic renal failure, prurigo nodularis and opioid-induced pruritus. The κ-opioid receptor agonist nalbuphine exhibited antipruritic activity in hemodialysis-related pruritus [18-21]. Nalbuphine, a mixed µ-receptor antagonist and κ-receptor agonist, appears more effective than naltrexone, since generalized pruritus reflects an imbalance between κ- and µ-opioid receptors [5].

Cannabinoid receptors are present in the CNS, peripheral nervous system (PNS), skin and on immune cells. Nerve cells and keratinocytes release endogenous cannabinoids. Cannabinoids suppress pruritus when bind to specific receptors [22]. Topical application of cannabinoids (e.g., N-palmitoylethanolamine) can reduce pruritus. Thus, different receptors coexist on a single fiber, concerning the polymodal nature of many primary neurons e.g., mechano-sensitive C-fibers express H1 and TRPV1 receptors and transmit itch; mechano-sensitive C-fibers express TRPV1 receptors (mediating pain and itch) and PAR2 receptors (mediate itch) and transmit pain and itch [5].

Pruritus can originate in the PNS, CNS or spinal cord. A specific GPCR, called mass-related G-protein coupled receptor X1 (mrgpr X1) that mediates chloroquine-induced pruritus and responds to PAR-2 agonists, was detected in a subset of human neurons in the DRGs. These neurons express gastrin-releasing peptide which is important in the transmission of itch [23].

Itch-specific pathways exist in the spinal cord [7]. Like C-fibers, the primary and secondary sensory neurons in the spinal ganglia are histamine-sensitive and histamine-insensitive [8]. From lamina 1 of the dorsal horn to the thalamic cortex, pruritus-specific sensory spinal neurons form the specific pathway. No pruritus-specific brain center/area has been detected. There are multiple sites in the brain with overlapping of pain and itch: anterior cingulate cortex, supplementary motor area, inferior parietal lobe. Functional differences were detected in pruritus: left hemispheric dominance; no activation of thalamic and somato-sensory cortex on parietal brain; predominant activation of ipsilateral motor areas; no subcortical activation [5].

### EPIDEMIOLOGY

According to a Norwegian population-based cross-sectional study from 2003, including more than 18,770 adults from Oslo, pruritus was the most prevalent of all reported skin symptoms. The prevalence of the acute itching (during one week) in adults was 8.4% and was worse for younger people aged 30 years (11.9% in females, 9.6% in males), decreasing with age for both genders [24]. In a survey done in the sample of 18.137 surveyed subjects, representative of the French population, the prevalence of perceived chronic
pruritus during 24 months prior to the survey was 12.4%, and the estimated current prevalence was 5.4% [25]. In a German pilot study which objective was to develop and validate an instrument that will measure prevalence and characteristics of chronic pruritus in general population, the point prevalence was 13.9%, annual 16.5%, and lifetime 22.6% [26]. In an African cross-sectional multi-country study made in order to assess the public-health importance of the onchocercal skin disease, 42% of population older than 20 years in highly endemic communities suffered from pruritus. The prevalence strongly correlated with the endemicity of cutaneous onchocerciasis which was measured by the prevalence of nodules in the studied population. Pruritus was more prevalent among those with lower household income and socio-economic status [27]. Patients with skin diseases exhibit a significant negative correlation between the level of psychosocial well-being and the prevalence of itch. Among depressed people the prevalence is significantly higher than in non-depressed, 18% versus 9%, respectively. Depressed patients have an elevated corticotrophin releasing factor in the cerebrospinal fluid, a major physiologic regulator of pro-opiomelanocortin-derived peptides, e.g. beta-endorphin [24, 28].

In age-specific populations, the following prevalences of chronic itch were estimated: 8.8% among adolescents [29]; 9% in pediatric dialysis patients; 22.2% in children on peritoneal dialysis [30]; 19.5% in patients older than 85 years. Chronic pruritus in elderly arises from the following: xerosis; increased mast cell degranulation; skin sensitivity to histamine, higher rate of comorbidity and drug-induced adverse effects that make them more susceptible [31]. We should substitute the term "senile", with an "inappropriately diagnosed" chronic pruritus.

Pruritus occurs in 18% of all pregnancies. Pruritus leads in intrahepatic cholestasis of pregnancy (ICP), being more prevalent in women on oral contraceptives, with personal history of cholestasis, multiple gestations, advanced maternal age. After viral hepatitis, ICP represents the second most common cause of gestational jaundice: the prevalence ranges from 1% (Europe) to 27.6% (Chile) [32].

**PRURITUS IN DERMATOLOGIC DISEASES**

In general practice, 50% of dermatological patients report pruritus as their main problem. Skin diseases are present in 57% of patients consulting dermatologists for chronic pruritus [33]. Pruritus represents a characteristic symptom not only in parasitic skin infestations, contact reactions, e.g., dermatitis [34], erythema multiforme [35] urticaria [36], atopic dermatitis [37], but also in psoriasis [38], venous insufficiency, bacterial, fungal, viral infections [39]; bullous diseases, neoplastic, e.g., cutaneous T-cell lymphoma. Drug-induced pruritus may start during the treatment of pruritus [40].

In one report, 87% of patients with the atopic dermatitis reported daily itching; in 65% of them pruritus was most frequent at night [41]. In atopic dermatitis, pathophysiology includes: free nerve endings; keratinocytes expressing neuropeptides; Th2-lymphocytes; mast cells; keratinocytes and eosinophils expressing neurotrophin NGF (nerve growth factor); ECP (eosinophil cationic protein); IL-31, and receptors H4, IL-31 and PAR2 [8].

Generalized pruritus was reported in 84% of patients with widespread psoriasis; daily occurrence was reported in 77% [42]. Szepietowski et al. [43] reported pruritus in 80% of patients: Psoriasis Severity Index (PSI) was significantly higher among patients with pruritus; in 81%, pruritus was confined to psoriatic lesions; it also involved non-lesional skin in 19%. Local lesion- limited inflammation implies peripheral origin of pruritus, whereas changes in neuropeptide distribution and in epidermal nerve fiber density suggest neuropathic origin! Vulvar psoriasis is significantly more common among women with vulvar pruritus [44]. In a questionnaire-based study in patients with the chronic plaque psoriasis, drying of the skin (80%) and stress (66%) were major pruritus-aggravating factors, while sleep, sun and holidays alleviated chronic pruritus [45]. Depression was the only significant predictor of pruritus in psoriasis and anger in chronic spontaneous urticaria [46]. Apart from histamine acting via H1 receptor, IL-31 and H4 receptors are important mediators in chronic urticaria [8].

Pruritus may follow several months post-burn in 87% of patients. Post-burn represents a scar and a consequence of nerve regeneration (NGF). In a recent investigation, the most significant predictors of pruritus were deep dermal injury and early post-injury stress-symptoms [47].

Pruritus may arise during bacterial, viral, and fungal infections and is usually acute. One third of patients with secondary syphilis have pruritus [4].

**PRURITUS IN SYSTEMIC DISEASES**

In dermatology departments, 10-50% of patients with pruritus, without obvious dermatologic cause, have an underlying systemic disease. However, if true relationship between the onset/course of both the pruritus and the disease was previously elucidated, such an association would vary between 4.3% and 22%; the most severe pruritus was in patients who had multiple systemic diseases; assessment of patients with chronic pruritus seldom reveals a preexisting unknown systemic disease responsible for pruritus [48, 49].

Investigations of patients with generalized chronic pruritus in France, Germany and Uganda revealed the prevalence of underlying systemic diseases of 40%, 36% and 0%, respectively. In France, the most common systemic disease was toxocariasis (8.4%) [33, 50].

**PRURITUS IN INFECTIOUS DISEASES**

In herpes zoster, chronic (post-herpetic) pruritus occurs in 4% of patients. Pruritus occurs more frequently if the head, neck or face is affected. Chronic pruritus occurs in 4.5% of patients with varicella [51].
Severe pruritus occurs in advanced HIV disease, and correlates with faster decline of CD4+ T-lymphocyte counts, thus it can be regarded as a cutaneous marker of disease progression [39]. In HIV-related diseases, pruritus may occur without skin disease, but it can frequently be associated with: scabies, seborrheic dermatitis, eczema; renal or hepatic disease, lymphoma; eosinophilic folliculitis, pruritic papular eruption, and prurigo nodularis. In Uganda 28% of dermatological patients have chronic pruritus, 70% are HIV-positive; among all HIV-tested patients with prurigo, 88% were positive [52]. Pruritus is mediated with cytokine-induced prostaglandin E_2, and the effect of the HIV-1 coat protein gp 120 on C-fibers in the skin, and on inflammatory axonal damage [53].

**PRURITUS IN CERTAIN INTERNAL DISEASES**

Due to improved technology (polysulphone membrane), pruritus affects not 85%, as a decade ago, but 38-55% of patients receiving dialysis. Pruritus is unrelated to sex, age, duration, cause of dialysis, a list of unproven suggestions: dry skin; mast cell proliferation; Th1 cytokines; secondary hyperparathyroidism; disturbed balance between µ-opioid and κ-opioid receptors; substance P; increased skin ions Ca^{++}, Mg^{++}, PO_4^{--}; abnormal transmission via the spine (gabapentin represents the first-line systemic therapy); serotonin, (mirtazapine represents the second-line therapy) [54, 55].

In cholestasis pruritus is generalized, migratory, typically triggered by tight clothing, not relieved with scratching: affecting 70% of patients with primary biliary cirrhosis, and 15% of hepatitis-C virus-positive patients. Since the prevalence of HCV-positivity in patients with chronic pruritus did not significantly differ from that in general population, it was proposed not to perform routine testing in the absence of risk factors [56].

In diabetes mellitus, generalized pruritus occurs in less than 10% of patients, which is not significantly higher than in non-diabetic patients. Localized pruritus in the perianal/genital region affects diabetic women more frequently and is significantly associated with poor diabetes control: in some, it may be the consequence of an increased predisposition to fungal infections [48, 57].

The relation between iron deficiency/replacement and chronic pruritus has to be questioned: no control trials have been conducted. There is no evidence supporting the routine determination of iron level in patients with vulvar/perianal pruritus. In polycythemia rubra vera, the history of chronic pruritus has been documented in 48% of patients: water-produced pruritus may precede development of disease by years; pruritus was significantly associated with high leukocyte count and lower blood cell mean corpuscular volume [57]. The exact pathomechanism includes: increased basophils; JAK2 617V>F-mutation; abnormal transmission via the spine [8]. Platelet aggregation has been proposed as a possible mechanism, leading to release of serotonin, and histamine. The treatment includes aspirin, paroxetine, H1-, H2-antihistamines.

Generalized pruritus affects 30% of patients with Hodgkin's lymphoma, 10% with non-Hodgkin's lymphoma (usually with cutaneous lesions). Localized pruritus affects 5% of patients with leukemia. Chronic pruritus precedes Hodgkin's lymphoma by years, if severe/persistent, predicts a poor prognosis, if recurs, it announces tumor recurrence. Pruritus in Hodgkin's disease is mediated by histamine, since it responses to cimetidine, but may follow cholestasis and disturbed central neurotransmission, since its beneficial response to mirtazapine [57, 58].

Chronic pruritus as a paraneoplastic sign, is present in 10% of patients exhibiting pruritus of “undetermined origin” (previously “idiopathic”), with lymphoma and leukemia being the most common malignancies. It is defined as pruritus that: precedes clinical appearance or occurs early during the natural course of the malignancy; is not provoked by mass invasion/compression; subsides after removal of the tumor. Pruritus is common in skin paraneoplastic syndromes: erythroderma (97%), dermatomyositis (18-32%), malignant acanthosis nigricans (41%); aquagenic pruritus (can precede development of T cell lymphoma or myelodyplasia by years). Some known/suggested factors include: histamine release from basophils; eosinophilia. Assessing the roles of IL-6, -8, -31 is a “timely topic” [49, 58].

**DRUG-INDUCED PRURITUS**

Drug-induced pruritus without skin lesions accounts for 5% of drug-induced cutaneous side-effects among hospitalized patients: it can start with the first dose or be delayed for several weeks/months: it resolves shortly after the drug has been discontinued or lasts for months/years after drug withdrawal. A clear time-relation has been estimated for some drugs: pruritus usually lasts in this group less than 6 weeks. Proposed pathomechanisms include: cholestasis, hepatotoxicity, sebostasis/xerosis, phototoxicity, neurologic mechanisms, deposition (pruritus after hydroxyethyl-starch deposition in the skin lasts 15 months without skin lesions) [4, 31, 58].

There are no epidemiological studies in long-term treatment with morphine and anti-malarials, including chronic drug-induced pruritus in pregnancy. The list of drugs inducing chronic pruritus includes: antihypertensives, antiarrhythmics, antiocoagulants, antidiabetics, hypolipemics, antibiotics, chemotherapeutics, psychotropic drugs, antiepileptics, cytokastics, cytokines, growth factors, monoclonal antibodies, plasma volume expanders and others [31, 57].

**PRURITUS IN NEUROLOGICAL DISEASES**

In a recent study, it has been reported that 17% of patients who were referred to dermatologists due to chronic itch and with no cutaneous lesions, had an underlying neurological disease [48]. Chronic pruritus may arise after neuronal damage, when it is termed neuropathic and should be differentiated from pruritus without neuronal damage, termed neurogenic pruritus. As generated in the central nervous system,
neurogenic pruritus represents a consequence of circulating metabolic or chemical (neurochemical pruritus) pathogens, such as pruritus in cholestasis or in response to intraspinal morphine injection [3, 5, 31]. It has been postulated that any damage along the afferent pathway of the nervous system can elicit chronic pruritus. Neuropathic pruritus is related to primary lesion/dysfunction located at any level along the afferent pathway of the nervous system. It is characterized by the association with other sensory symptoms-signs (pain, paresthesia/hyperesthesia) in a dermatome, or motor or autonomic damage. Pathomechanisms of neuropathic itch are still incompletely elucidated, but several are proposed: local nerve damage; central neuronal deprivation of afferent input, when central itch neurons fire due to increased tone in descending pathways that leads to diminishing of itch traffic; central sensitization; long-term changes in cortical somatosensory pathways. Sensitization of nerve fibers may be peripheral and central. Central sensitization (allokinesis) of nerve fibers is implicated in the majority of cases of neuropathic itch. The phenomenon of central sensitization is explained by the excitation of secondary transmission neurons in the dorsal root spinal ganglia due to continuing activation of C-fibers. Since abnormal transmission via the spine has been proposed, antiepileptic drug – gabapentin, a structural analogue of the inhibitory transmitter γ-aminobutyric acid, represents the first-line systemic therapy in almost all cases of neuropathic itch [5, 13].

Neuropathic pruritus may arise due to peripheral nerve lesions and the central nerve system lesions [5, 13]. More than a half of all patients with postherpetic neuralgia, which is a prototype of peripheral neuropathy, have pruritus. Apart from postherpetic, other types of peripheral sensitization may provoke pruritus such as brachioradial pruritus (compression of the cervical C2-C8 nerve root); notalgia paresthetica (trauma/entrapment of the thoracal T2-T6 nerve root); cheiralgia paresthetica (entrapment of the radial nerve); trigeminal trophic syndrome (ablation of the Gasserian ganglion); pruritus in keloids, burn and postmastectomy scars; anogenital pruritus in lumbosacral radiculopathy. Central nervous system lesions include spinal cord and brain pathologies (tumors, strokes abscesses, multiple sclerosis). The paroxysmal spontaneous pruritus or that triggered by movement, which often awakes patient, occurs in 5% of cases with multiple sclerosis: mediated by impaired synaptic conductivity, rather than by demyelination [13].

According to Jeffrey D. Bernhard [3], terms neurogenic and neuropathic should be considered synonymous.

PRURITUS IN PSYCHIATRIC/PSYCHOSOMATIC DISEASES – SOMATOFORM PRURITUS

If onset of pruritus is temporarily connected with significant psychopathology (anxiety, depression, schizophrenia), it is a psychogenic or somatoform pruritus. It represents a psychosomatic definition of “pruritus sine materia”, a diagnosis of exclusion. It can occur with another type of pruritus or/and along with a preexisting psychopathology. It is present in 2-12% of patients visiting dermatologists without primary skin disease [48, 59]. Depression, psychogenic parasitosis, obsessive-compulsive disorder, anxiety, somatoform disorders, psychosis, substance abuse were reported with pruritus: somatoform pruritus may accompany comorbidities of psychiatric and psychosomatic diseases. Diagnostic criteria that do not include obligatory psychiatric disease have been proposed: 3 compulsory (all must be met) and 7 optional (at least 3 must be present). Compulsory criteria include localized/generalized pruritus: without primary skin lesions; lasting for more than 6 weeks; without somatic cause. Optional criteria are: chronologic relationship with one/several life events that could have psychologic repercussions; variations in intensity associated with stress; nocturnal variations; predominance during rest/inaction; association with psychologic disorders; improvement by psychotropic drugs; improvement by psychotherapy [60-63].

Depression may be the primary condition in somatoform pruritus. Depressed patients have elevated levels of corticotrophin-releasing factor in cerebrospinal fluid that may decrease the threshold for pruritus by increasing the central nervous opiate levels [28].

The secondary skin lesions are found on areas accessible to the hands. There are three types of psychogenic excoriations: obsessive-compulsive (neurotic and those in delusions of parasitosis, affecting middle-aged women, fully aware of what they are doing; impulsive, in anxious and depressive disorders; and mixed. According to Arnold, psychogenic pruritus is a prototype of impulsive excoriations, however, could also develop without any skin signs [13, 59].

Beside many advances in our comprehension of pathophysiology and treatment of pruritus, inconsistencies are still present "when thinking about the most prominent and Zen-like of dermatological symptoms – itch, an invisible sensation in the most visual of medical specialties". [3].

CLASSIFICATION

Clinically-based classification of pruritus is proposed by the International Forum for the Study of itch [60]. The first part classifies the underlying conditions according to groups I-III (Table 1). Primary skin lesions may be confounded by secondary [60, 64]. Primary skin lesions and secondary (reactive to scratching/rubbing) must be differentiated in, for example, atopic dermatitis. The second part classifies the underlying conditions according to etiology in different categories I-IV (Table 1). Category V or

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<td><strong>Groups of patients</strong></td>
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<td><strong>Classification of diseases</strong></td>
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<td><strong>Group I: pruritus on primary diseased skin</strong></td>
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<td><strong>Group II: pruritus on non-diseased skin</strong></td>
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<td><strong>Group III: chronic secondary scratch lesions</strong></td>
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“mixed” includes patients with more than one underlying disease that may be responsible. Category VI or “pruritus of undetermined origin” includes chronic pruritus without finding of underlying origin.

In management of patients with chronic pruritus, first they should be grouped according to clinical picture/history. Second, they should be classified on the basis of laboratory/histological/radiological findings (Table 1) [60].

CONCLUSION

Pruritus is prevalent in the general population. Pruritus and pain have their own neuronal pathways with wide interactions. The proposed classification distinguishes between pruritus with and without primary or secondary skin lesions and should be considered as the only segment of a comprehensive approach to pruritus of unknown origin. Thus, persistent pruritus without obvious dermatologic pathology should encourage investigation for the underlying systemic cause.

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КРАТАК САДРЖАЈ
Откривањем медиатора и рецептора специфичних за прурутиус постављен је неуровербални концепт прурутиуса који је одликовао: Ц унормени специфични за сврб хистамин и хистамин-независни процеси; радионики специфични за сврб кутаним и спиналним нервним коридорима. Укључиви функционални „дијалог“ између неуровербалних специфичних за прурутиус и његове структуре стимулације и реакције које се осредњавају на специфични прурутиусу. У складу са формулацијом специфичних за прурутиус и функционалним интеракцијама, прурутиус уколико је компликован, зависи од саставних делова, али код 10-50% особа које немају обољење коже је манифестација системског поремећаја. Издање прурутиуса у оквиру аутоимунских и унапредних болести у дерматолошкој заснива се на клиничкој слици и природи основног обољења и подразумева појаву прурутиуса на примарно и/или секундарно инфилтрираној кожи. Прурутиус у интерпретацији медицине преновљен подразумева прурутиус у примарно незначајном односно кожи са законским факторима који се појављују на кожи. Класификација прурутиуса обједињује етиологије типа Рисуна и примене, на којима је заснована научна група са проблемами коже у нервнастим системским поремећајима. У складу са формулацијом специфичних за прурутиус и функционалним интеракцијама, прурутиус уколико је компликован, зависи од саставних делова, али код 10-50% особа које немају обољење коже је манифестација системског поремећаја. Издање прурутиуса у оквиру аутоимунских и унапредних болести у дерматолошкој заснива се на клиничкој слици и природи основног обољења и подразумева појаву прурутиуса на примарно и/или секундарно инфилтрираној кожи. Прурутиус у интерпретацији медицине преновљен подразумева прурутиус у примарно незначајном односно кожи са законским факторима који се појављују на кожи. Класификација прурутиуса обједињује етиологије типа Рисуна и примене, на којима је заснована научна група са проблемами коже у нервнастим системским поремећајима. У складу са формулацијом специфичних за прурутиус и функционалним интеракцијама, прурутиус уколико је компликован, зависи од саставних делова, али код 10-50% особа које немају обољење коже је манифестација системског поремећаја. Издање прурутиуса у оквиру аутоимунских и унапредних болести у дерматолошкој заснива се на клиничкој слици и природи основног обољења и подразумева појаву прурутиуса на примарно и/или секундарно инфилтрираној кожи. Прурутиус у интерпретацији медицине преновљен подразумева прурутиус у примарно незначајном односно кожи са законским факторима који се појављују на кожи. Класификација прурутиуса обједињује етиологије типа Рисуна и примене, на којима је заснована научна група са проблемами коже у нервнастим системским поремећајима. У складу са формулацијом специфичних за прурутиус и функционалним интеракцијама, прурутиус уколико је компликован, зависи од саставних делова, али код 10-50% особа које немају обољење коже је манифестација системског поремећаја. Издање прурутиуса у оквиру аутоимунских и унапредних болести у дерматолошкој заснива се на клиничкој слици и природи основног обољења и подразумева појаву прурутиуса на примарно и/или секундарно инфилтрираној кожи. Прурутиус у интерпретацији медицине преновљен подразумева прурутиус у примарно незначајном односно кожи са законским факторима који се појављују на кожи. Класификација прурутиуса обједињује етиологије типа Рисуна и примене, на којима је заснована научна група са проблемами коже у нервнастим системским поремећајима. У складу са формулацијом специфичних за прурутиус и функционалним интеракцијама, прурутиус уколико је компликован, зависи од саставних делова, али код 10-50% особа које немају обољење коже је манифестација системског поремећаја. Издање прурутиуса у оквиру аутоимунских и унапредних болести у дерматолошкој заснива се на клиничкој слици и природи основног обољења и подразумева појаву прурутиуса на примарно и/или секундарно инфилтрираној кожи. Прурутиус у интерпретацији медицине преновљен подразумева прурутиус у примарно незначајном односно кожи са законским факторима који се појављују на кожи. Класификација прурутиуса обједињује етиологије типа Рисуна и примене, на којима је заснована научна група са проблемами коже у нервнастим системским поремећајима. У складу са формулацијом специфичних за прурутиус и функционалним интеракцијама, прурутиус уколико је компликован, зависи од саставних делова, али код 10-50% особа које немају обољење коже је манифестација системског поремећаја.