

Topical Hypochlorous Acid (HOCl) as a Potential Treatment of Pruritus

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Abstract Topical hypochlorous acid (HOCl) has recently been proposed as a treatment of pruritus. However, it is not known whether topical HOCl decreases or promotes pruritus. This review sheds light on this poorly understood subject. This article describes the pathophysiology of pruritus, current treatments of pruritus, and how pH determines the properties of HOCl in solution. The article then proposes two mechanisms by which HOCl may reduce pruritus: 1) HOCl is microbicidal to cutaneous pathogens, especially *Staphylococcus aureus* in atopic dermatitis; 2) HOCl is anti-inflammatory and reduces the activities of histamine, leukotriene B₄, and interleukin-2, all of which are implicated in the pathophysiology of itch. Lastly, this article describes conditions under which HOCl may actually cause pruritus as an adverse effect. For example, HOCl increases the activity of nerve growth factor, which promotes itch. Prolonged or high-dose HOCl exposure may also cause irritant contact dermatitis, or less commonly, allergic contact dermatitis.

Keywords Hypochlorous acid · HOCl · Hypochlorite · NaOCl · Bleach · Itch · Pruritus · Treatment · Therapy · Topical · Atopic dermatitis · *Staphylococcus aureus* · Bactericidal · Microbicidal · Inflammation · Histamine · Leukotriene B₄ · Interleukin-2 · Nerve growth factor ·

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Contact dermatitis · Irritation · pH · Allergic ·
Hypersensitivity · Urticaria

Introduction

Pruritus is the most common symptom seen in dermatologic disease and has a significantly negative impact upon patient quality of life [1•, 2••]. Recently, topical hypochlorous acid (HOCl) has been proposed as a treatment of pruritus [3••]. However, it is not known definitively whether topical HOCl decreases or promotes pruritus, because so little research has been published on this topic to date [3••]. This review article sheds light on this subject by combining information from current literature on pruritus and literature on HOCl. This article consists of five parts. The first discusses the pathophysiology of itch, while the second discusses current treatments of itch. The third part of this review explains how the properties of HOCl in solution depend strongly on the solution's pH. In the fourth part, using available literature on pruritus and literature on HOCl, we propose the following two mechanisms by which HOCl may reduce pruritus: 1) HOCl is microbicidal to cutaneous pathogens, especially *Staphylococcus aureus* in atopic dermatitis [3••]; 2) HOCl is anti-inflammatory and reduces the activities of histamine, leukotriene B₄ (LTB₄), and interleukin-2 (IL-2), all of which have been implicated in the pathophysiology of itch [1•, 4•, 5, 6•]. Lastly, in the interest of patient safety, we describe conditions under which HOCl may actually cause pruritus as an adverse effect. For example, HOCl increases the activity of nerve growth factor (NGF), which promotes itch [4•, 5]. Prolonged exposure or high doses of HOCl may also result in irritant contact dermatitis, and less commonly in allergic contact dermatitis (which is a Type IV hypersensitivity reaction). This stresses the importance of delivery in order to translate HOCl to the bedside [7].

Pathophysiology of Itch

Pruritus is defined as an uncomfortable sensation that causes the wish to scratch [2••, 4•]. Pruritus is sensed in the epidermis (whose removal completely stops cutaneous itch sensation), mucous membranes, or cornea, but no other tissue types [5]. Acute itch lasts from seconds to 1 week, whereas chronic itch lasts for more than 6 weeks and is the subject of this paper [2••]. There are four types of itch: Psychogenic, neurogenic, neuropathic, and pruritoceptive pruritus [1•, 4•]. Each type of itch is described below.

Psychogenic pruritus is an urge of psychiatric etiology to scratch physically normal skin, and is a diagnosis of exclusion [1•]. Psychogenic itch can be associated with psychological disorders, such as somatoform disorders, substance abuse, psychosis, mania, depression, stress, anxiety, obsessive compulsive disorder, and delusional parasitosis [1•, 2••, 4•].

Neurogenic itch is pruritus whose afferent pathway includes the central nervous system (CNS), but neurogenic itch is always secondary to disease occurring outside of the skin [1•, 4•, 8]. These diseases include hematologic disorders (e.g., polycythemia vera), lymphoproliferative diseases (e.g., leukemia, Hodgkin lymphoma, Sezary syndrome), cholestasis (often due to hepatic disease), endocrine diseases, chronic kidney disease (CKD), or iatrogenic opioid-induced pruritus [1•, 2••, 4•, 8]. In contrast to neuropathic pruritus, neuronal damage does not play a role in the pathophysiology of neurogenic pruritus [1•]. Possible etiologies of neurogenic itch include pruritogens in the bloodstream (e.g., cholestatic pruritus) or endogenous intraspinal opioids [1•, 4•].

Neuropathic itch is pruritus due to damage to peripheral or central neurons located anywhere in the afferent pathway of itch sensation, resulting in over-activation of the itch pathway that is independent of normal stimuli for itch [1•, 4•]. For example, damage to C-fibers might cause an increase in their firing rate, thereby over-activating the afferent itch pathway [1•]. Alternatively, a lesion might cause neurons in the spinothalamic tract that normally inhibit itch sensation to decrease their firing rate [1•]. Neuropathic itch is rarely relieved by scratching and often occurs concomitantly with paresthesia, hypoesthesia, or hyperesthesia [1•]. Neuropathic itch can be secondary to post-herpetic neuralgia, notalgia parasthetica, brachioradial pruritus, peripheral nervous system (PNS) tumors, or CNS tumors [1•, 4•].

Pruritoceptive itch is pruritus due to stimuli in the epidermis, which activate the entire afferent pathway of itch sensation [1•]. This pathway is triggered when compromised function of the epidermal skin barrier (which occurs more commonly at night), inflammation, or age-related skin changes cause release into the epidermis of pruritogens [1•, 2••, 5]. These pruritogens bind to and activate receptors on

the termini of free nerve endings of C-fibers in the epidermal stratum granulosum [1•, 5, 9]. It is unknown whether this occurs in C-fibers alone, or if keratinocytes are similarly activated and then interact with adjacent C-fibers [1•, 5]. Table 1 lists some of these receptors expressed in the epidermis by C-fibers and possibly by keratinocytes, their corresponding pruritogenic agonists, and associated pruritic diseases whose pathogenesis involves these receptor-agonist pairs [1•, 4•, 5, 10]. Note that HOCl reduces the activities of three of these pruritogenic agonists (histamine, LTB₄, and IL-2), but increases the activity of one of them (NGF) [1•, 4•, 5, 6•]. The sensory neurons that project these C-fibers peripherally have their somas located in the dorsal root ganglia and project axons centrally into the spinothalamic tract [1•]. After activation of any of the receptors listed in Table 1, the afferent itch signal travels through these sensory neurons, through the spinothalamic tract to the thalamus, and to the somatosensory cortex [1•, 4•, 8].

Current Treatment of Itch

Currently, treatment of pruritus is based on only a small number of studies with small sample sizes, which are mostly case series, usually without controls, and usually not double blinded [2••]. Table 2 summarizes currently available treatments of chronic pruritus, their mechanisms of action, pruritic diseases in which they are indicated, and common adverse effects. Topical treatments are used for mild or localized pruritus, whereas systemic treatments are used for severe or generalized pruritus [2••]. If an underlying cause of pruritus can be identified, then treating the causative disease often decreases the pruritus [2••].

The Properties of HOCl in Solution Depend Upon pH

The properties of HOCl in solution are strongly linked to the solution's pH. This is because pH changes can cause HOCl to react, resulting in mixtures of HOCl in equilibrium with various reaction products [11]. Therefore, evaluation of the biochemical and clinical effects of HOCl should, whenever possible, take into account the pH and reaction products with which HOCl is in equilibrium [12]. One problem with the current literature on HOCl is that pH is often not considered.

In aqueous 0.9 % Na⁺ Cl⁻ solution (which has the same osmolality as human plasma [13]), pH changes cause HOCl to react as follows [11]:

When pH < 3.5, decreases in pH drive forward the following three reactions (displayed below with their equilibrium constants), in which HOCl reacts and forms Cl₂ (aq), Cl₂ (g),

Table 1 Receptors that mediate itch, corresponding pruritogenic agonists, associated pruritic diseases whose pathogenesis involves the receptor–agonist pair, and agents to treat itch that target the receptor or the agonist [1•, 2••, 4•, 5, 10, 26, 27, 37, 38, 40]

Receptor	Pruritogenic agonist	Associated with pruritus in the following diseases	Agent used to treat itch
Receptors expressed in the epidermis by C-fibers (and possibly by keratinocytes):			
H1 GPCR ^a	Histamine	Urticaria	1st and 2nd generation H1 antihistamines ^b , doxepin ^c
H4 GPCR ^a	Histamine	Urticaria	N/A
Nicotinic acetylcholine-gated cation channels ^a	Acetylcholine	Atopic dermatitis	N/A
Muscarinic GPCRs ^a	Acetylcholine	Atopic dermatitis	N/A
Leukotriene B4 (LTB4) GPCR ^a	Leukotriene B4 (LTB4)	Atopic dermatitis	Zileuton ^d
Neurokinin 1 (NK1) GPCR ^a	Tachykinins, including: Substance P	Atopic dermatitis, psoriasis, Sezary syndrome	Aprepitant ^c
Interleukin-2 receptor (IL-2R) ^a	Interleukin-2 (IL-2)	Atopic dermatitis	Cyclosporine ^e , topical calcineurin inhibitors (tacrolimus and pimecrolimus) ^e
Interleukin-31 JAK-linked receptor (IL-31R) ^a	Interleukin-31 (IL-31)	Atopic dermatitis, prurigo nodularis, familial primary localized cutaneous amyloidosis	Anti-IL-31 antibody
Protease-activated receptor-2 (PAR2) GPCR ^a	Several different proteases ^f , including: Kallikreins, tryptase, cathepsin S, protease allergens from dust mites and cockroaches, and cowhage	Atopic dermatitis	Topical agents with low pH decrease serine protease activity, decreasing PAR2 activity
TRP vanilloid receptor-1 (TRPV1) ligand-gated ion channel ^g	Unknown	Prurigo nodularis	Capsaicin ^h
Tropomyosin-related kinase A (TrkA) receptor tyrosine kinase ⁱ	Nerve growth factor (NGF)	Atopic dermatitis, psoriasis, prurigo nodularis	N/A
Prostanoid receptors ^j	Prostaglandin E (PGE), thromboxane A ₂ (TxA ₂)	Atopic dermatitis	Topical or oral salicylates ^k
Intraspinal receptors:			
Increased μ-opioid GPCR activity (which promotes itch) relative to κ-opioid GPCR activity (which inhibits itch)	Opioid peptides	Cholestatic pruritus, iatrogenic opioid-induced pruritus, atopic dermatitis	Naloxone ^l , naltrexone ^l , nalmefene ^l , butorphanol ^m

GPCR denotes a G protein coupled receptor;

^a This receptor triggers the itch pathway upon binding agonist; ^b Receptor inverse agonist; ^c Receptor antagonist; ^d Acts by decreasing leukotriene B4 synthesis; ^e Acts by decreasing IL-2 synthesis; ^f This list includes serine proteases whose activity is increased by high epidermal pH (eg. due to high pH in antibacterial soap) and decreased by low epidermal pH; ^g Does not trigger itch, but TRPV1 expression is necessary for histamine and serotonin to cause itch; ^h Acts by binding to TRPV1 of C-fiber, causing depletion of neuropeptides in that C-fiber; ⁱ Does not trigger itch, but decreases itch threshold of skin; ^j Does not trigger itch, but sensitizes other receptors to itch; ^k Acts by inhibiting cyclooxygenase (COX), thereby decreasing synthesis of prostanoids, including PGE and TxA₂; ^l μ-opioid antagonist; ^m Combined μ-opioid antagonist and κ-opioid agonist

and Cl₃⁻ (aq) [11]. Therefore, when pH < 3.5, decreases in pH result in a mixture of decreasing concentrations of HOCl (aq)

and increasing concentrations of Cl₂ (aq), Cl₂ (g), and Cl₃⁻ (aq) [11]:

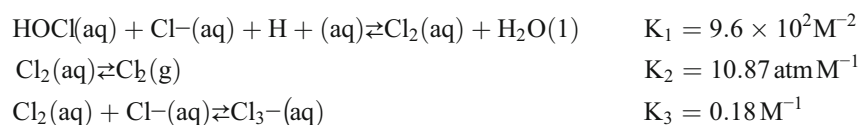


Table 2 Current treatment of chronic pruritus [1•, 2••, 4•, 5, 38–40]

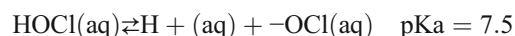
Agent	Mechanism of action in treating itch	Indicated for pruritus in the following diseases	Adverse effects
Topical agents for itch: ^a			
Moisturizers, emollients, barrier repair creams	Improves function of the epidermal skin barrier	AD ^b , itch due to dry skin, nocturnal pruritus	N/A
Menthol (1–3 %) cream or lotion	Agonist of TRPM8 ligand-gated ion channel, which causes cooling sensation	Any case of pruritus that is relieved by cooling sensation	Menthol concentrations above 1–3 % can cause irritation.
Topical salicylates (2–6 %)	Inhibits PG ^c synthesis	Neurodermatitis	CI ^d in children and acute inflammatory dermatoses
Topical glucocorticoids ^e	Decreases inflammation of skin	Inflammatory dermatoses only (e.g. AD ^b , psoriasis)	Skin atrophy, telangiectasia, HPA ^f suppression.
Topical calcineurin inhibitors (TCIs): Tacrolimus ointment or pimecrolimus cream	Decreases IL-2 synthesis; TRPV1 ^g may also be involved.	AD ^b , PN ^h , irritant contact dermatitis, anogenital pruritus, graft versus host disease, lichen sclerosis	Stinging and burning sensations
Doxepin (5 %) cream	Has H1 GPCR antagonist activity	AD ^b , contact dermatitis, nummular dermatitis, neurodermatitis	Burning sensation, allergic contact dermatitis, sedation. CI ^d in children.
Lidocaine (5 %) patch	Local anesthetic	Neuropathic pruritus	N/A
Topical pramoxine (1 %)	Local anesthetic	CKD ⁱ , facial pruritus	N/A
Topical polidocanol (3 %)+urea (5 %)	Local anesthetic and moisturizer	AD ^b , contact dermatitis, psoriasis	N/A
Capsaicin (.025-.1 %) cream	Binds to TRPV1 ^g of C-fiber, causing depletion of neuropeptides in C-fiber	PN ^h , aquagenic pruritus, CKD ⁱ , neuropathic itch.	Intense burning sensation during the first few days of treatment
N-palmitoylethanolamine cream	CB2 cannabinoid receptor agonist	AD ^b , PN ^h , neurodermatitis, CKD ⁱ	N/A
Systemic agents for itch:			
Oral 1st and 2nd generation H1 antihistamines	H1 GPCR inverse agonist	Urticaria	1st generation H1 antihistamines: Sedation.
Oral salicylates	Inhibits PG ^c synthesis	Polycythemia vera	N/A
Aprepitant	NK1 ^j GPCR antagonist	Sezary syndrome	N/A
Intravenous lidocaine (5 %)	Anesthetic	Cholestatic pruritus	N/A
Mirtazapine	Antagonist of the following receptors: alpha2, 5-HT2, 5-HT3, H1	Nocturnal pruritus, AD ^b , Leukemia, lymphoma, CKD ⁱ , cholestatic pruritus	Increased appetite, weight gain, sedation
Paroxetine or fluvoxamine	SSRI ^k	AD ^b , paraneoplastic itch	N/A
Sertraline	SSRI ^k	Cholestatic pruritus	N/A
Gabapentin	Inhibits transmission of afferent itch signal to brain	Neuropathic itch, CKD ⁱ , Sezary syndrome	Drowsiness, weight gain. CI ^d in cholestatic pruritus
Naltrexone or nalmefene	μ-opioid GPCR antagonist	Cholestatic pruritus, CKD ⁱ , AD ^b , urticaria, burns	Nausea, vomiting, drowsiness
Butorphanol	μ-opioid antagonist and κ-opioid agonist activity	Nocturnal pruritus, intractable pruritus	Nausea, vomiting, drowsiness
Nalfurafine	κ-opioid GPCR agonist	CKD ⁱ	Insomnia
Oral cyclosporine ^e	Decreases IL-2 synthesis	Refractory itch in AD ^b	HTN ^l , nephrotoxicity, immunosuppression
Oral azathioprine ^e	Toxicity to lymphocytes	Refractory itch in AD ^b	Myelosuppression

GPCR denotes a G protein coupled receptor

^aNote that any topical agent with low pH can decrease pruritus by decreasing activity of serine proteases, thereby decreasing activation of protease-activated receptor-2 (PAR2) GPCR; ^bAtopic dermatitis; ^cProstanoid; ^dContraindicated; ^eProlonged duration of use is contraindicated; ^fHypothalamus-anterior pituitary-adrenal cortex axis; ^gTRP vanilloid receptor-1 ligand-gated ion channel; ^hPrurigo nodularis; ⁱChronic kidney disease; ^jNeurokinin 1 GPCR; ^kSelective serotonin reuptake inhibitor; ^lHypertension

At pH between 3.5 and 5.5, HOCl is stable [11].

When $\text{pH} > 5.5$, increases in pH drive forward the following reaction (displayed below with its pK_a), in which HOCl is deprotonated and forms $-\text{OCl}(\text{aq})$ [11]. Therefore, when $\text{pH} > 5.5$, increases in pH result in a mixture of decreasing concentrations of HOCl (aq) and increasing concentrations of $-\text{OCl}(\text{aq})$ [11]:



In general, HOCl is more reactive than $-\text{OCl}$ [12]. Therefore, relative to $-\text{OCl}$, HOCl is more powerful as an irritant of skin, antimicrobial agent, and stain remover when used on laundry in commercial bleach [12]. Solution containing HOCl and $-\text{OCl}$ in equilibrium is often made by dissolving sodium hypochlorite (NaOCl) in H_2O . Therefore, the sum of the concentrations of HOCl and $-\text{OCl}$ is often quoted as % NaOCl , which equals 100 times the ratio of the mass of NaOCl dissolved in solution to the total mass of solution [14].

Mechanisms by which HOCl May Decrease Pruritus

To date, the only clinical study specifically testing the effect of topical HOCl treatment on severity of pruritus is a recent poster by Draelos et al. [3••]. In this case series (which lacked controls), 20 human subjects with atopic dermatitis received 7 days of treatment with topical hydrogel containing 0.008 % HOCl and 0.002 % NaOCl [3••, 15]. Severity of pruritus was measured using a visual analogue scale reported by subjects, a 5-point ordinal scale reported by subjects, and a 5-point ordinal scale reported by the investigator [3••]. By all measurements taken, there was a statistically significant decrease in severity of pruritus at day 3 of treatment [3••]. During days 4–7, skin barrier repair foam

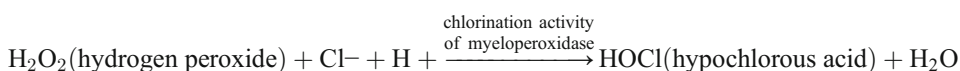
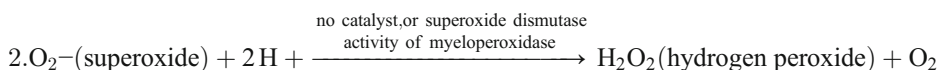
was included in the treatment regimen, and further reductions in pruritus were reported [3••].

Despite these promising results, it is not known definitively whether HOCl decreases or promotes pruritus, because so little research has been published on this topic to date [3••]. Moreover, if HOCl is anti-pruritic, its exact mechanism of action has yet to be elucidated [3••]. However, by correlating the current body of knowledge on pruritus with information on HOCl, we propose mechanisms by which HOCl may have anti-pruritic effects, as well as conditions under which HOCl may actually cause pruritus as an adverse effect. Specifically, HOCl may reduce pruritus by either of the following two mechanisms: 1) HOCl is microbicidal to cutaneous pathogens, especially *Staphylococcus aureus* in atopic dermatitis [3••]; 2) HOCl is anti-inflammatory and reduces the activities of histamine, LTB_4 , and IL-2 , all of which have been implicated in the pathophysiology of itch [1•, 4•, 5, 6•]. However, interestingly, HOCl increases the activity of NGF, which enhances itch [4•, 5]. Moreover, prolonged exposure or high doses of HOCl may promote pruritus by causing irritant contact dermatitis, or less commonly, allergic contact dermatitis (which is a Type IV hypersensitivity reaction) [7].

Microbicidal Activity of HOCl

HOCl may reduce pruritus because it is microbicidal to cutaneous pathogens that exacerbate pruritic diseases, especially *Staphylococcus aureus* on the skin of atopic dermatitis patients [3••].

The microbicidal effect of HOCl plays a central role when HOCl is produced during the human innate immune response. When myeloperoxidase-expressing cells (including neutrophils, monocytes, and, under certain conditions, macrophages [16, 17]) phagocytose pathogens, HOCl is produced in the phagosome by the respiratory burst pathway, which consists of the following three reactions [6•, 11, 18•]:



The resulting HOCl undergoes reactions with various functional groups of proteins, including chlorination of amino groups and oxidation of thiol groups of cys residues, thioether groups of

met residues, disulfide groups, trp residues, and heme groups [11, 18•, 19, 20]. These reactions make HOCl microbicidal, because, among other antimicrobial mechanisms, they damage

the electron transport chain and cause depletion of adenine nucleotides [18•, 21]. When most of the bactericidal activity occurs, pH=7.4–7.8 in the phagosome [18•]. HOCl has pKa of 7.5, so this pH range implies by the Henderson-Hasselbalch equation that the [HOCl]/[-OCl] ratio in the phagosome is between 1.3(=10^{7.5-7.4}) and 0.50(=10^{7.5-7.8}) when most bacteria are killed [11, 22]. Concentrations between 0.169 and 2.73 µg/mL of HOCl are microbicidal in vitro to fungi, such as *Candida albicans*, and to many species of bacteria, including methicillin-sensitive (MSSA) and methicillin-resistant (MRSA) *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, *Streptococcus pyogenes*, vancomycin-resistant *Enterococcus faecium*, *Serratia marcescens*, *Escherichia coli*, *Enterobacter aerogenes*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Haemophilus influenzae* [11, 19].

Staphylococcus aureus overgrowth on skin is the most common cause of exacerbation of atopic dermatitis [23••]. This exacerbation occurs partly because *S. aureus* releases superantigens, which increase inflammation in skin lesions [23••]. Therefore, disease severity of atopic dermatitis can be reduced if the amount of *S. aureus* on the skin is decreased [23••]. Use of antibiotics increases the likelihood of development of bacterial drug resistance [23••]. Therefore, bleach baths, in which low concentrations of NaOCl are dissolved in bathwater, are a potential alternative or adjuvant treatment to decrease cutaneous *S. aureus* levels [23••]. The review by Barnes et al. [23••] summarizes the four clinical studies published to date, providing evidence that dilute bleach baths ranging from 0.004 to 0.016 % NaOCl (used concomitantly with intranasal mupirocin) reduce severity of disease in atopic dermatitis complicated by *S. aureus* overgrowth on skin [23••].

Net Anti-Inflammatory Effect of HOCl

HOCl might decrease pruritus by reducing inflammation. HOCl has both anti-inflammatory effects and pro-inflammatory effects, which are described immediately below [19]. Altogether, the anti-inflammatory effects outweigh the pro-inflammatory effects, so that the net effect of HOCl is anti-inflammatory [19]. This net anti-inflammatory effect by itself may reduce pruritus [2••]. We emphasize that HOCl reduces the activities of several pro-inflammatory chemical messengers that have been implicated in the pathophysiology of itch (See Table 1), including histamine (associated with urticaria), LTB₄ (associated with atopic dermatitis), and IL-2 (associated with atopic dermatitis) [1•, 4•, 5, 6•]. However, we also note that HOCl increases the activity of NGF, which promotes itch and is associated with atopic dermatitis, psoriasis, and prurigo nodularis [4•, 5].

HOCl has multiple anti-inflammatory effects, including the following:

- 1) HOCl adds one or more Cl groups to the NH₂ group of histamine, thereby converting histamine to a histamine-N-chloramine and decreasing the activity of histamine [6•, 19].
- 2) Oxidation by HOCl of thiol or thioether groups directly decreases the activity of leukotrienes released by neutrophils (including sulfidopeptidic-leukotriene C₄-sulfoxide and 6-trans-leukotriene B₄) and of interleukin-6 (IL-6) [6•, 19].
- 3) Oxidation by HOCl of thiol or thioether groups directly increases the activity of transforming growth factor-beta (TGF-beta), which is anti-inflammatory [19, 24].
- 4) Oxidation by HOCl of thiol groups may cause phosphorylation and hence activation of receptor tyrosine kinases, which causes increased synthesis of growth factors [19].
- 5) At high concentrations, HOCl decreases the activities of the following proteases: matrix metalloproteinase-7 (MMP-7) (because HOCl oxidizes adjacent trp and gly residues at the catalytic site of MMP-7), collagenases (if the HOCl/collagenase ratio >40), and possibly gelatinases (if the HOCl/gelatinase ratio >30) [19]. We could not find information on whether matrix metalloproteinases (MMPs), collagenases, or gelatinases are agonists of the protease-activated receptor-2 (PAR2), whose activation has been implicated in the pathophysiology of itch (as discussed in Tables 1 and 2) [1•, 2••, 4•, 5]. However, we note that the PAR2 receptor is activated by a diverse array of proteases (See Table 1) [1•, 5]. If MMP-7, collagenases, or gelatinases are PAR2 agonists, then the reduction in their activities in response to high HOCl concentrations might be another mechanism by which HOCl could reduce pruritus.
- 6) Alpha2-macroglobulin is a plasma protein that binds to and neutralizes signaling molecules [19]. HOCl oxidizes alpha2-macroglobulin, which causes an increase in the binding affinity (and hence neutralizing activity) of alpha2-macroglobulin for pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-alpha), IL-2, and IL-6 [6•, 19]. Oxidation by HOCl of alpha2-macroglobulin also decreases the binding affinity (and hence neutralizing activity) of alpha2-macroglobulin for growth factors, including beta-nerve growth factor (beta-NGF), platelet-derived growth factor-BB (PDGF-BB), TGF-beta1, and TGF-beta2 [19].
- 7) HOCl chlorinates proteinaceous parts of antigens, which causes decreased activity of the innate immune system against Gram positive bacteria, but increased activity against Gram negative bacteria [19].

As mentioned above, HOCl also has several pro-inflammatory effects:

- 1) Whereas high concentrations of HOCl decrease protease activities, low concentrations of HOCl increase the activities of the following proteases by oxidizing the thiol groups of their cys residues: MMPs, collagenases (if the HOCl/collagenase ratio < 40), and gelatinase B [19]. As mentioned above, we were not able to find any information on whether MMPs, collagenases, or gelatinases agonize the PAR2 receptor or cause pruritus.
- 2) Oxidation by HOCl of alpha2-macroglobulin may also decrease the binding affinity (and hence neutralizing activity) of alpha2-macroglobulin for cell proteases [19]. Again, we do not know whether these cell proteases agonize the PAR2 receptor or are associated with pruritus.
- 3) Oxidation by HOCl of met residues might also increase activity of c5 of the complement pathway [19].
- 4) HOCl increases binding of macrophages to endothelium and increases permeability of blood vessels by increasing the size of spaces between endothelial cells [19, 25].
- 5) Oxidation by HOCl of thiol groups may cause phosphorylation and hence activation of receptor tyrosine kinases, which causes increased synthesis of pro-inflammatory cytokines [19]. We could not find information on whether this process also phosphorylates and activates receptor tyrosine kinases that promote pruritus, such as the IL-31 receptor or the tropomyosin-related kinase A (TrkA) receptor (See Table 1) [1•, 4•, 5, 26, 27]. However, if they are activated, then this might be a mechanism by which HOCl could actually increase pruritus.

Safety of HOCl: Conditions Under which HOCl May Promote Pruritus as an Adverse Effect

HOCl can promote pruritus as an adverse effect under certain conditions, which should be taken into account to ensure patient safety. As mentioned above, HOCl increases the activity of NGF, which promotes itch and is associated with atopic dermatitis, psoriasis, and prurigo nodularis (See Table 1) [4•, 5]. Topical HOCl treatment may also exacerbate pruritus because high-dose or prolonged cutaneous HOCl exposure can cause skin diseases of which pruritus is a principal symptom [7, 28]. Among these pruritic diseases, irritant contact dermatitis is most common, followed by allergic contact dermatitis (which is a Type IV hypersensitivity reaction to cutaneous HOCl exposure) [7, 28]. Even rarer are cases of Type I hypersensitivity reaction to cutaneous or systemic HOCl exposure, of which immunologic contact urticaria (ICU) is the major symptom [7, 28, 29]. Both the Type IV and Type I HOCl-induced hypersensitivity reactions occur following initial sensitization to HOCl, which can happen in response to high-dose or prolonged cutaneous or systemic exposure to

HOCl (during which the patient may experience irritant contact dermatitis) [7]. In addition to rare instances of Type I hypersensitivity reaction, rare cases of HOCl-induced non-immunologic contact urticaria (NICU) have been reported [7, 28, 29]. Therefore, before treatment with HOCl is initiated, it is recommended that the patient receive an open skin test or a skin prick test, in order to detect HOCl-induced Type I hypersensitivity reaction (including ICU) or HOCl-induced NICU [7, 29]. If the test result is negative, the patient should then be patch tested for HOCl-induced Type IV hypersensitivity reaction [7, 12]. In these tests, avoid using high concentrations and/or volumes of HOCl, which can cause irritant contact dermatitis, resulting in false positive test results [12].

Irritant Contact Dermatitis (ICD) due to HOCl

HOCl is a well-known cause of irritant contact dermatitis (ICD) [28]. As demonstrated by several clinical studies, the degree of skin irritation in HOCl-induced ICD depends upon duration of cutaneous exposure to HOCl and -OCl, the combined amount of HOCl and -OCl to which a given area of skin is exposed, and the pH of the HOCl solution in the epidermis.

Duration of HOCl exposure and HOCl concentration play significant roles in the pathogenesis of HOCl-induced ICD, as demonstrated by Goffin et al. [30] in a double-blind, placebo-controlled trial of 15 adult female human subjects with normal skin [30]. Damage to the stratum corneum is often the first step in the pathogenesis of ICD [30]. Goffin et al. [30] provided evidence that this is true in HOCl-induced ICD by showing that damage to the stratum corneum (but probably not more deeply located parts of the skin) caused the first subclinical signs of cutaneous irritation following HOCl patch testing of brief but varying durations (ranging from 15 to 90 minutes) [30]. Longer duration of HOCl exposure and higher HOCl concentration increased stratum corneum damage, thereby increasing the severity of these initial subclinical signs [30]. For example, longer duration of cutaneous exposure to 4 % NaOCl solution caused an increase in squametry index *in vivo*, indicating decreased strength of adhesion between corneocytes in the stratum corneum [30]. Longer duration of exposure to 4 % NaOCl solution may have also reduced skin capacitance *in vivo*, indicating loss of H₂O from the stratum corneum [30, 31]. *Ex vivo* corneometry also showed that solutions with higher % NaOCl had increased reactivity with the stratum corneum [30]. Unfortunately, the relationship between pH of HOCl solution and stratum corneum damage was not explored by Goffin et al. [30] and requires further study.

As mentioned above, the combined amount of HOCl and -OCl to which a given area of skin is exposed is a significant determinant of the degree of skin irritation seen clinically. In a

non-blinded, controlled trial of 50 adult human subjects without skin disease, Hostynek et al. [12] evaluated degree of skin irritation (measured both by a 5-point visual erythema scale and by red hue detected by a skin color reflectance meter) following a 24-hour patch test in which HOCl solutions of varying pH levels and varying volumes were applied to a given area of skin [12]. The sum of the molar concentrations of HOCl and -OCl (which we denote as C) was held constant at 1.36×10^{-7} mol/ μ L (which is equivalent to 1 wt % NaOCl) [12]. This study found that degree of skin irritation is an increasing function of the volume of HOCl solution applied to the skin area under the patch (V_{patch}) [12]. Other reports indicate that degree of skin irritation is also an increasing function of C [23••, 32]. Values of C corresponding to % NaOCl above 0.5 % can cause irritation [33, 34]. We believe that the following hypothesis generalizes these results: Skin irritation is an increasing function of the combined number of moles of HOCl and -OCl applied to a given area of skin ($C \times V_{\text{patch}}$).

The pH of the HOCl solution in the epidermis is another important determinant of the degree of skin irritation. We define pH_{max} as the pH of HOCl solution in the epidermis at which skin irritation reaches a maximum. Hostynek et al. [12] determined that, when $C \times V_{\text{patch}}$ is held constant at 1.36×10^{-7} mol/ μ L \times 100 μ L, then $\text{pH}_{\text{max}} \approx 8$ [12]. When pH in the epidermis rises above $\text{pH}_{\text{max}} = 8$, skin irritation decreases because HOCl, which is more irritating to skin (because it is more reactive, as mentioned above), is deprotonated and forms -OCl, which is less irritating to skin [12]. When pH in the epidermis decreases below $\text{pH}_{\text{max}} = 8$, the decrease in pH itself becomes the dominant factor and causes a reduction in skin irritation [12]. We speculate that the decrease in skin irritation occurs because lower pH in the epidermis results in decreased activity of serine proteases, thereby decreasing activation of the PAR2 receptor (which is discussed in Tables 1 and 2) [2••, 5, 35]. We also suspect that pH_{max} is not constant at 8, but instead depends upon $C \times V_{\text{patch}}$. For example, when $C \times V_{\text{patch}}$ is held constant at a very low level near 0, then, at any given pH, a marginal *increase* in pH will have a small irritation-reducing effect by converting HOCl to -OCl and a large irritation-increasing effect by raising pH. This implies that pH_{max} (where these two effects balance each other) will be very high. In the extreme case, when $C \times V_{\text{patch}} = 0$, then pH_{max} is infinitely high. However, when $C \times V_{\text{patch}}$ is held constant at a very high level, then, at any given pH, a marginal *decrease* in pH will have a large irritation-increasing effect by converting -OCl to HOCl and a small irritation-reducing effect by lowering pH. This implies that pH_{max} (where these two effects balance each other) will be very low. In the extreme case, when $C \times V_{\text{patch}}$ approaches infinity, then pH_{max} is infinitely negative. Based on this reasoning, we propose the following hypothesis: pH_{max} is a decreasing function of $C \times V_{\text{patch}}$.

The buffering capacity of the skin is another significant determinant of the degree of skin irritation in HOCl-induced ICD. The skin's buffering capacity causes basic HOCl solutions to have pH in the epidermis that is lower than their ex vivo pH and acidic HOCl solutions to have pH in the epidermis that is higher than their ex vivo pH [12, 36]. However, the magnitude of this buffering effect decreases if the buffering capacity is overcome, which can occur due to any of the following: 1) very high amounts of basic or acidic solution are applied to a given area of skin (that is, $C \times V_{\text{patch}}$ is very high); 2) solutions with very high ex vivo pH or very low ex vivo pH are applied to skin [12]. If pH_{max} is within the buffer range of the skin, then the skin's buffering capacity pulls the pH of the HOCl solution in the epidermis closer to pH_{max} , thereby increasing skin irritation [12]. In this case, skin irritation may paradoxically decrease if the skin's buffering capacity is overcome either by high $C \times V_{\text{patch}}$ or by extremes of ex vivo pH [12]. If pH_{max} is outside of the buffer range of the skin, then the skin's buffering capacity pulls the pH of the HOCl solution in the epidermis farther away from pH_{max} , thereby decreasing skin irritation [12]. In this case, skin irritation increases if the skin's buffering capacity is overcome either by high $C \times V_{\text{patch}}$ or by extremes of ex vivo pH [12].

Conclusion

Using available literature on pruritus and literature on HOCl, we have proposed mechanisms by which HOCl may have anti-pruritic effects, as well as conditions under which HOCl may actually cause pruritus. HOCl may reduce pruritus either through its microbicidal effects upon cutaneous pathogens (especially *Staphylococcus aureus* in atopic dermatitis [3••]) or through its anti-inflammatory effects (especially reduction in the activities of histamine, LTB₄, and IL-2, all of which have been implicated in the pathophysiology of itch [1•, 4•, 5, 6•]). However, HOCl may promote pruritus by increasing the activity of NGF [4•, 5]. Prolonged exposure or high doses of HOCl may also promote pruritus as an adverse effect by causing irritant contact dermatitis, or less commonly allergic contact dermatitis (which is a Type IV hypersensitivity reaction) [7]. Currently, there is a dearth of available research on the relationship between HOCl and pruritus, and we look forward to future studies that will test and elaborate on the hypotheses proposed in this paper.

Compliance with Ethics Guidelines

Conflict of Interest RY Pelgrift declares no conflicts of interest. AJ Friedman declares no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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