Prevalence, pathophysiology and management of itch in epidermolysis bullosa*

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Summary
Epidermolysis bullosa (EB) is a highly diverse group of inherited skin disorders, resulting from mutations in genes encoding proteins of the dermoepidermal junction. Itch (pruritus) is one of the most common symptoms across all EB subtypes. It occurs in blistered or wounded sites, or manifests as a generalized phenomenon, thereby affecting both intact skin and healing wounds. The mechanism of pruritus in EB is unclear. It is likely that skin inflammation secondary to barrier disruption, wound healing cascades and dysregulated activation of epidermal sensory nerve endings are all involved in its pathophysiology on the molecular and cellular level. Understanding these mechanisms in depth is crucial in developing optimized treatments for people with EB and improving quality of life. This review summarizes current evidence on the prevalence, mechanisms and management of itch in EB.

Introduction
Epidermolysis bullosa (EB) is a diverse group of inherited skin disorders caused by defects in proteins of the dermoepidermal junction and within the epidermis. Thousands of pathogenic variants in at least 16 different genes have been associated with classical EB.1 The inheritance pattern is either autosomal dominant or recessive, while many cases also arise de novo.

Classical forms of EB are classified into four main types depending on the level of blistering within the cutaneous basement membrane zone;1 EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB) and Kindler EB (KEB). DEB is further divided into dominant (DDEB) and recessive (RDEB) forms.1

Itch (pruritus) is a common symptom across all EB subtypes and affects both intact skin and healing wounds,5 with several internal or external contributory factors (Figure 1).3–5 Pruritus triggers a vicious itch–scratch cycle that exacerbates skin irritation, leading to new blister formation, worsens existing wounds and potentially increases the risk of infections.6 Itch in EB may start from as early as birth and is associated with a great burden in terms of quality of life (QoL) and also an economic burden on patients.7 Its major impact on QoL is also reflected in its association with depression, anxiety, social isolation, financial difficulties and even suicidal ideation in a large number of other dermatological conditions.8

Methods
This review summarizes the prevalence, clinical burden, pathobiology and therapies for pruritus in EB of all types. We searched PubMed for all peer-reviewed articles published to date, written in English and containing the keywords ‘epidermolysis bullosa’, ‘epidermolysis bullosa pruriginosa’, ‘itch’, ‘pruritus’ and ‘inflammation’. In view of the paucity of evidence on EB-related pruritus, an effort was made to include all retrieved relevant publications.

What is known about mechanisms of itch in the skin?

There is growing evidence that itch is the result of a dysregulated interplay between keratinocytes, immune cells and
sensory nerves, triggered by endogenous or exogenous pruritogens.\textsuperscript{9–12} Chronic itch is transmitted by histaminergic and/or nonhistaminergic nerve C-fibres. Histamine is involved in acute or chronic urticaria via the histamine-1 receptor,\textsuperscript{13} and may play a role in histamine-4 receptor-mediated itch.\textsuperscript{14} Additionally, numerous nonhistaminergic itch mediators and receptors have been recently identified.\textsuperscript{13,15} These mediators pertain to several categories such as proteases, neuropeptides, prostaglandins, cytokines and lipids, which activate mostly high-affinity receptors on peripheral sensory nerve endings. Some of these ligands are also capable of activating promiscuous receptors at micromolar concentrations (low affinity). Keratinocytes and immune cells also express receptors for various itch mediators; activation of such receptors leads these cells to release further pruritogens thus enhancing the itch response.\textsuperscript{16} Of particular interest are proteinase-activated receptors (PAR)-2 and PAR-4, cytokine receptors (e.g. interleukin (IL)-4, IL-13, IL-31, thymic stromal lymphopoietin (TSLP)), ion channels (e.g. TRPV1, TRPV3, TRPV4, TRPM8, TRPA1) and mediators linked to G protein-coupled receptors such as histamine, prostaglandins or leukotrienes.\textsuperscript{15,17,18} A plethora of central mediators involved in itch have also been identified in the spinal cord, including opioids, gastrin-releasing peptide, brain-derived natriuretic peptide, glutamate, neurokinin-1, bradykinin, serotonin, somatostatin and histamine receptors.\textsuperscript{12,19} Apart from central transmission of itch signalling, cutaneous nerve fibres release neuromediators that bind to immune cells or keratinocytes, causing them to release yet more pruritogens that again bind to itch-selective nerve fibres and further amplify the pruritic neuronal signal.\textsuperscript{15,20–22}

In chronic itch, perpetuated inflammation and prolonged exposure of sensory nerves to itch mediators is believed to cause neuronal hypersensitivity to itch stimuli, or in other words, peripheral sensitization.\textsuperscript{15} There is also evidence that reduction in epidermal innervation density and loss of descending inhibition from the central nervous system contribute to the chronicity of pruritus.\textsuperscript{23}

How common is itch in epidermolysis bullosa?

Few studies have investigated the prevalence of itch in EB. In a survey of 40 adults with either of the three major EB types (EBS, JEB or DEB), 85% reported itch, a prevalence similar to that found in atopic dermatitis (AD).\textsuperscript{6,24} Other aspects such as frequency, duration and severity were also comparable with those in AD. The highest prevalence was noted in individuals with JEB (100%) and RDEB (100%), followed by DDEB (87%) and EBS (74%).\textsuperscript{4} Results were similar in a survey of 146 US patients of all ages and all EB types. Itch was rated as the most troublesome symptom, above pain, eating problems and wound infections. Its frequency increased with self-reported disease severity, being the highest in RDEB (average of 3.9 on a 5-point Likert scale).\textsuperscript{25} Healing wounds and the surrounding skin, infected wounds and dry skin were significantly more itchy than non-wounded skin or scars, and the incidence of pruritus was highest in body areas with the greatest number of wounds.

Itch was also ranked as the top concern in semistructured interviews involving 10 children with EB.\textsuperscript{26} Again, children with more severe disease ranked itch higher in their list of concerns. A Korean cross-sectional study of 13 patients with RDEB of severe or intermediate type also assessed pruritus using a visual analogue scale (VAS).\textsuperscript{7} The mean VAS score in RDEB was 7.54 ± 2.07, which is considered severe itch. VAS scores were higher in severe than in intermediate RDEB, and were also higher in ‘very severe’ than in ‘severe’ disease as self-reported by patients on the 5-point patient global assessment.

In line with these findings, the Spanish DEB Priority Setting Partnership has identified itch as one of the three main research needs in EB.\textsuperscript{27}

What is the pathophysiology of itch in epidermolysis bullosa skin?

The mechanism of pruritus in EB is unclear. Several aspects of EB pathophysiology are likely to be involved (presented in Figure 2).
Inflammation and epidermolysis bullosa skin

Inflammation is a prominent feature of EB skin. Numerous articles in the peer-reviewed literature highlight the presence of inflammatory infiltrates in EB skin (Table S1; see Supporting Information). In particular, there are reports of eosinophilic infiltrates in skin biopsies across all EB types, observed both in the blister cavities and in the upper dermis (Figure 2).28–31 Interestingly, this pattern of eosinophilic infiltration is similar to that which occurs in bullous pemphigoid (BP), where subepidermal blistering occurs secondary to autoantibodies principally against the hemidesmosomal antigen BP180 (collagen XVII).32,33 Itch severity in BP was shown to correlate with the number of dermal eosinophils, the epidermal expression of neurokinin-1 receptor (NK1R), IL-31RA, oncostatin M receptor-β and the expression of T helper (Th) 2-associated mediators, including IL-4, IL-13 and periostin.34 In the same study, TSLP expression was increased in BP lesions, but this did not correlate with itch severity. IL-4, IL-13 and TSLP are potent pruritogens.21,22,35 Skin fragility with associated severe itch and increased TSLP levels were also described in a mouse model of dysfunctional BP180 (which causes inherited defects that lead to localized and intermediate forms of JEB in humans).36

There is plenty of evidence suggesting dysregulation of Th1, Th2 and Th17 cytokines in EB skin, many of which are also implicated in pruritus. One study compared culture media from keratinocytes carrying mutant keratin 14 with wildtype keratinocytes and found increased levels of tumour necrosis factor (TNF)-α (Figure 2; box A),37 which has been implicated in both acute and chronic itch in mice.38,39 Other investigators demonstrated an increase in the proinflammatory...
Role of wound healing in epidermolysis bullosa-associated itch

Healing wounds and the surrounding skin are known to be more itchy than intact skin. A plethora of proinflammatory cytokines are released during the early stages of wound healing, including TNF-α, IL-2, IL-4, IL-6 and IL-8 (Figure 2; box A). There is evidence that chronic wounds contain increased levels of proinflammatory cytokines, particularly TNF-α and IL-1β. These, and products of the inflammatory cascades that they initiate, might not only mediate the recruitment of immune cells to the wounded site (Figure 2; box B2), but also directly activate sensory neurons, triggering itch signals or even increasing the neurons’ responsiveness to pruritogens (Figure 2; box E). In turn, sensory fibres in the skin release neurotransmitters, including substance P, calcitonin gene-related peptide, brain-derived natriuretic peptide and nerve growth factor, all of which are implicated in pruritus pathophysiology (Figure 2; box F).

The concept that the wound healing process triggers pruritus is supported by observations that this is a major problem in patients with burns. The prevalence of pruritus in this group is over 90% at the time of discharge from hospital, just below 90% at 6 months and gradually reduces with time to approximately 70% at 2 years postburn, while the intensity correlates with the total burned surface area and also reduces with time.

Impaired skin barrier function in epidermolysis bullosa

There is a well-established association between skin barrier dysfunction and itchy skin. Thus, it is of interest whether EB-related mutations may affect the expression of molecules that are involved in preserving skin barrier integrity. In six patients with EBS, gene expression analysis of the epidermis in normal-appearing skin compared with an equal number of controls identified 28 differentially expressed genes; the majority of these were implicated in fatty acid metabolism or the structural organization of the epidermis, which are both pertinent to the synthesis and integrity of the cornified cell envelope. Analogous differences in gene expression were identified in vitro between EBS cell lines and wildtype control keratinocytes. Barrier dysfunction resulting from such modifications in genetic expression could make skin vulnerable to environmental pruritogens and lower the threshold for itch. However, direct evidence for this hypothesis is still lacking for EB-associated itch.

Simultaneous reduction in collagen XVII and filaggrin expression in the skin has been reported in one case of JEB. However, it is noteworthy that only the four prevalent filaggrin mutations (p.R501X, c.2382del4, p.R2447X and p.S3247X) were excluded in this individual, which does not exclude the possibility of less common filaggrin variants.

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The special case of epidermolysis bullosa pruriginosa

The extremely itchy subtype of DEB is known as DEB pruriginosa (DEB-P). This is a rare clinical entity, which was first described in 1994. Patients in this subgroup are affected by severe pruritus, often since birth (although onset can be delayed by several decades), associated with a distinctive phenotype, with extensive lichenified nodules and plaques, mostly on the lower legs and often in a linear distribution (Figure 3).

Approximately 200 cases of DEB-P have been reported worldwide in the literature. All are caused by mutations in the gene encoding collagen VII (COL7A1), the main component of the anchoring fibrils. Inheritance is dominant in most, but recessive and sporadic cases have also been reported.

What is the anecdotal and case-report evidence for the treatment of epidermolysis bullosa itch?

Addressing pruritus is crucial for the successful management of EB. Various environmental, pharmacological and behavioural interventions are available, which are summarized in Table 1. Nonetheless, these remain empirical and often unsatisfactory.

In a US study of 146 patients with EB of all types, ointments (53-4%), lotions (45-2%), creams (40-4%) and oral hydroxyzine (39-0%) were the most frequently used anti-itch treatments. Expert recommendations include non-sedating H-1 blockers for the management of daytime itch vs. sedating H-1 antihistamines or tricyclic antidepressant medications with prominent anti-H-1 activity for night itch, combined with the appropriate choice of dressings. Biosynthetic cellulose dressings and hydrogel sheets are favoured for itchy wounds, followed by foams and modified absorbent pads. Short courses of topical corticosteroids and neuropathic agents can be used as second line to antihistamines.

Evidence in the literature for systemic pharmacological agents is largely limited to case reports or series. Good responses to oral ciclosporin have been described in several DEB cases; clinical benefits were seen within 2 weeks to 2 months of treatment. Anecdotal case reports also claim successful treatment with the topical calcineurin inhibitor tacrolimus and with thalidomide in DEB-P, cannabinoid-based sublingual medicines in JEB and RDEB, and dapsone in EBS.

Most importantly, newer biological agents are making their way into EB treatment with some encouraging results. The anti-IL-4Rα monoclonal antibody dupilumab improved pruritus in a recent case of DEB-P. Its use led to a significant reduction in the itch VAS score from 9 to 5 and a reduction in Dermatology Life Quality Index score from 23 to 8, by week 12 of treatment. Apremilast, an inhibitor of phosphodiesterase-4 and thus Th17 activation, reduced blistering in three cases of severe EBS, following mRNA analyses indicating Th17 cytokine overexpression in blisters, although the authors did not comment directly on its effect on pruritus. Clinical improvement, with reduction in chronically eroded areas, has also been reported in two DEB cases treated with TNF inhibitors (adalimumab and etanercept) for concomitant arthritis.
Clinical trials carried out to treat epidermolysis bullosa itch

There are only few clinical trials investigating novel therapies for EB itch. A placebo-controlled study of the neurokinin-1 antagonist serlopitant in DEB and JEB showed greater median itch reduction compared with placebo from baseline to week 4 on post hoc analysis. The efficacy of serlopitant for the treatment of pruritus of various other aetiologies has previously been demonstrated.

Improvement in wound healing with an associated reduction in pruritus was recently reported with the use of low-
dose topical calcipotriol in a double-blind placebo-controlled study of nine individuals with RDEB, following earlier in vitro data suggesting that calcipotriol enhances the local antimicrobial defence in RDEB keratinocytes.

Another phase I/IIa clinical trial using gene-corrected autologous epidermal sheets in seven participants with RDEB showed that the percentage of itchy wounds was reduced from 61% at baseline to 19% at 1 year post-treatment observation. The percentage was even lower at 2 years (7%) and 3 years (0%), and this was associated with a sustained improvement in patient-reported wound healing and pain.

Cell therapy may also have a positive impact on the severity of pruritus in RDEB; a prospective, phase I/II, open-label study using intravenous bone marrow-derived mesenchymal stromal/stem cells in 10 adults with RDEB showed a reduction in three of six itch dimensions compared with baseline, as determined by the Leuven Itch Scale.

Finally, treatment of chronic wounds in six patients with RDEB with reconstituted natural purified type I collagen skin substitutes led to a statistically significant reduction in pruritus post-treatment, as assessed using the VAS.

There are currently ongoing trials assessing the effect of serlopitant (NCT03836001) and pregabalin (NCT03928093) in EB pruritus, while a further trial of topical cannabinol (INM-755 cream) is in preparation (https://www.inmedpharma.com/science/inm-755-for-epidermolysis-bullosa/).

**Future strategies for improving understanding and developing better treatments for itch in epidermolysis bullosa**

**Elucidating itch at the molecular level**

Understanding pruritus at the molecular level is necessary to improve clinical management and should be a research priority for EB. Itch mechanisms might be distinct in different types of EB. The question remains as to whether and how EB pruritus is linked with inflammatory and wound healing cascades in the skin. Elucidating and targeting these pathways in each EB type might be a sensible approach, similar to itch transcriptome studies recently performed in psoriasis and atopic eczema, with the potential to reduce inflammation and promote wound healing simultaneously. Newer, multomic approaches can complement traditional laboratory techniques in this respect and facilitate hypothesis generation.

**Advancing to larger well-designed clinical trials**

There is a striking paucity of clinical trials focused on EB-related itch, despite this being one of the most problematic aspects of the condition. One challenge is the recruitment of adequate numbers of participants, owing to the rarity of the condition, which could be addressed via multicentre trials. A thorough assessment of pruritus in the context of such trials is also crucial in order to demonstrate clinically meaningful improvements, as pruritus is a symptom with complexity comparable with pain. Most existing studies have used the rather simplistic visual or numerical scales (VAS and Numeric Rating Scale, respectively), which solely score the severity of itch on a scale of 0–10 at the time of completion. A multidimensional approach that assesses other aspects, including frequency, duration, triggers, change with time and the effect on daily activities is best suited; some good examples include the 5-D and Leuven itch scales.

**Introducing and promoting targeted therapies in epidermolysis bullosa treatment**

Dermatology has entered a new exciting era of targeted biological therapies, some of which have shown very encouraging results in pruritus of other aetiologies, including atopic eczema, psoriasis and prurigo nodularis. Many of these biological therapies have a well-established safety profile through large-scale trials in other diseases. Most are relatively rapid-acting systems, which offer the added benefit of bypassing the practical challenges of topical applications, while also being less costly and easier to access than gene or cell therapies.

There are limited data on the role of biologics in the treatment of EB, and only a single clinical trial of a targeted agent (serlopitant). Existing evidence on the prominent role of inflammation in EB skin, along with encouraging results from the use of agents such as dupilumab and TNF inhibitors all provide support for trialling such drugs on a larger scale.

**Conclusions**

Pruritus is one of the most common and distressing symptoms in EB, and it has been consistently ranked as one of the top concerns for patients. Its intensity seems to correlate well with disease severity. Addressing this symptom effectively has the potential to provide major improvements in patients’ QoL and the overall quality of EB care. Despite this ambition, available treatments for EB-related pruritus are limited and often unsatisfactory, and there is very little by way of clinical trials of anti-itch agents.

More research to elucidate the molecular signature of pruritus in EB is pivotal to proceed with such trials. This will allow us to progress from merely symptomatic relief to specific pathway targeting, improved therapeutic efficacy and potentially more favourable safety profiles. Finally, insight into pruritus, inflammation and wound healing in the context of EB has the potential to teach us useful lessons applicable beyond this rare inherited skin disorder.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher’s website:

Table S1 Summary of in vitro animal and human studies in the worldwide literature highlighting immune cells and mediators of inflammation in epidermolysis bullosa.