

# Progress in the treatment of Hailey-Hailey disease

Wei Jiang, Xueyong Wang, Nan Li, Shan Li, Zhiguo Xu\*

Department of Dermatology, The 78th group army hospital of Chinese PLA, Mudanjiang, 157000, China

\* Corresponding author: Zhiguo Xu (570963755@qq.com)

**Abstract:** Familial benign chronic pemphigus, also known as Hailey-Hailey disease, is an autosomal dominant disease having genetic features that follow Mendelian inheritance principles. HHD is a rare disease that affects approximately one out of every 50,000 people. Clinically, it presents as blisters, fissures, erosions, and vegetations with significant pruritus or pain in skin folds or reversal areas of the skin. In the presence of heat, localized sweating, or exercise, patients with HHD may suffer repeated or worsened symptoms. Furthermore, concurrent bacterial, fungal, and viral infections may aggravate localized lesions. HHD may raise the likelihood of problems such as insomnia, anxiety, and depression. There are no treatment guidelines or large clinical trials for HHD. This could be attributed to the low prevalence of HHD. Although the pathogenesis of HHD is well understood, there are no specific or curative treatment options available. The majority of current treatment focuses on symptomatic relief. In this article, we will discuss the most recent advancements in HHD research.

**Keywords:** Hailey-Hailey disease; Familial benign chronic pemphigus; Treatment.

## 1. Introduction

Familial benign chronic pemphigus (FBCP), commonly known as Hailey-Hailey disease (HHD), is a rare skin disorder discovered in 1939 by the Hailey brothers<sup>1</sup>. The disease is caused by a mutation in the ATP2C1 gene on chromosome 3, which results in defective intracellular Golgi calcium transport and, as a result, decreased epidermal keratinocyte adhesion function<sup>2</sup>. Acantholysis or "dilapidated brick wall" can be seen on histopathological examination of HHD. Recurrent blisters, erosion, hyperplasia, and crusting intertriginous regions are typical clinical symptoms, together with intense local pruritus or severe pain (Fig. 1). If the lesions are infected, local malodorous vegetations may develop<sup>3</sup>. Although the pathophysiology of HHD is well established, no specific treatment or treatment is available, and there are no treatment guidelines to follow. In this paper, we will discuss the most recent research advances in the treatment of HHD, including traditional medications, invasive procedures, and biologic agents.



Figure 1. Inflammatory and erosive plaques on the inguinal.

## 2. Conventional Treatment

HHD clinical randomized controlled trials are scarce. A substantial number of treatments have been reported as case series or case reports. Many treatment options may lack evidence-based guidance. Our article focuses primarily on current therapies that have been shown to be effective.

### 2.1. Corticosteroids

Topical glucocorticoids can rapidly control the lesions' local inflammatory cascade<sup>5</sup>. Improving local lesions can also be accomplished by improving the local pruritic-scratch response. Burge et al. reported that topical application of moderate and high potency hormonal creams (mometasone furoate, clobetasone, halomethasone, etc.) can control the progression of lesions in the majority of patients with HHD<sup>6</sup>. Because of the superior efficacy of topical glucocorticoids, systemic glucocorticoids are not currently recommended for the treatment of HHD. During topical glucocorticosteroid application, local adverse effects such as skin atrophy, hyperpigmentation, increased infection risk, or skin hypertrichosis must be noted.

### 2.2. Anti-microbial drugs

Microbial colonization and infection of HHD lesions can result in a vicious cycle<sup>7</sup>. Microorganisms that cause microbial infections include viruses, bacteria, and fungi. Based on local lesion secretion cultures, PCR tests, staining of secretion slides, serologic tests, and clinical presentation, the specific microbial type of infection can be identified. Staphylococcus aureus, Candida albicans, and herpes simplex virus infections are all common causes of localized lesions infections<sup>4</sup>.

Gentamicin is an aminoglycoside that may treat HHD by acting through antibacterial action and eukaryotic transcriptional regulation<sup>8</sup>. Gentamicin has a promising application in genetic skin diseases, according to a case report study, by inducing transcriptional read-through of nonsense mutations<sup>8</sup>. This

study provides encouraging data that gentamicin for the treatment of HHD, palmoplantar keratosis, and dystrophic

maculopapular epidermolysis bullosa. More randomized controlled clinical trials on the efficacy of gentamicin are needed to determine its precise function. Gentamicin is primarily recommended for topical use to prevent ototoxicity and nephrotoxicity caused by systemic administration.

### 2.3. Calcineurin Inhibitors

The therapeutic mechanism of calcineurin inhibitors achieves therapeutic effects by regulating T-cell immune activity and mitotic proliferation. It has a wide range of applications in the head, face and skin folds. Topical glucocorticoids have more side effects than topical calcium inhibitors. Tacrolimus or pimecrolimus applied topically is more effective in treating inflammatory skin conditions like atopic dermatitis. Through case studies, Georgi et al. discovered that topical application of pimecrolimus ointment resulted in greater efficacy with HHD<sup>4</sup>. According to Arora et al., better results were also found when 0.1% tacrolimus ointment was applied topically. RCT trials, however, are required to further clarify these results.

### 2.4. Vitamin D Analogs

There are few case reports of carbatriol or tacalcitol being applied topically to treat HHD. Aoki et al. discovered that topical application of tacalcitol was more efficient than betamethasone<sup>9</sup>. Two case reports discovered that topical application of carbatriol ointment (2 times/day for 3 months) achieved complete remission of the lesions. However, Guarino et al. found no significant effect of vitamin D analogs in the treatment of HHD.

### 2.5. Retinoids

Retinoids (acitretin, isotretinoin) mainly exhibit therapeutic effects by modulating keratinocyte differentiation. Oral acitretin (10-25mg/dose for 3-5 months) was found to be effective in controlling HHD by Naidoo et al. Mashiko et al. discovered that oral Etretinate (60mg/dose for 2 weeks) was effective for control of HHD. There have also been case reports of isotretinoin being effective in the treatment of HHD. However, the therapeutic efficacy of these drugs is inconclusive, which limits their use in the treatment of HHD.

### 2.6. Naltrexone

Lauren et al. discovered that a low dose of naltrexone (3 mg/day for 1-2 weeks) given to patients with HHD effectively promoted local lesion healing<sup>10</sup>. Opioid receptors have been shown to be expressed on the surface of epidermal keratinocytes and to play an important role in wound healing. Naltrexone may exert its therapeutic effect by inhibiting epidermal Keratinocyte  $\mu$ -opioid receptors. Adverse effects of Naltrexone include: headache, gastrointestinal reactions and excessive dreaming. It is important to note that Naltrexone, as an opioid, may cause withdrawal symptoms or other side effects.

## 3. Invasive procedures

### 3.1. Carbon Dioxide Laser

Carbon dioxide lasers, which produce a laser with a wavelength of 10,600 nm, are effective in localized skin treatment. McElroy et al. discovered that the carbon dioxide laser was effective in improving HHD when used in a local exfoliation mode<sup>4</sup>. This condition is primarily for patients who have had poor results with conventional topical

medications or with localized lesions of hyperplasia.

### 3.2. Photodynamic therapy

In patients with HHD, Ruiz-Rodriguez et al. used ALA and laser irradiation (590-700 nm for 30 minutes) to treat local lesions. The lesions generally began to heal after 10 days and were free of recurrence during the 19-25 months of follow-up. The majority of the current case reports on the treatment of HHD with photodynamic therapy are case series reports. The adverse reactions of photodynamic therapy are mainly local erythema and blister formation.

### 3.3. Dermabrasion

Dermabrasion's main goal is to promote and stimulate local dermal remodeling by physically destroying the local epidermis through manipulation, thereby improving HHD. Moreover, for patients with malodorous vegetations lesions, we can actually consider using dermabrasion.

### 3.4. Skin grafting

Skin grafting is an option for patients with HHD who have not responded well to conventional therapy. Autologous skin grafts may be considered a common surgical technique. Recurrence of the disease, localized scarring, or hyperpigmentation are common side effects.

## 4. Biological agents

### 4.1. Tumor Necrosis Factor- $\alpha$ Inhibitors

Hurd et al. successfully used alefacept to treat a patient with HHD who did not respond well to conventional medications. Norman et al. used etanercept to treat a patient successfully with HHD<sup>4</sup>. The patient was initially given etanercept subcutaneously at a dose of 25 mg/week (for 1 month). The dose was then increased to 50 mg/week (for 6 months). Finally, the dose was titrated to 75 mg/week. The patient's condition gradually improved. The conclusions for treating HHD with TNF-inhibitors are primarily based on case reports. More clinical trials are needed to determine efficacy.

### 4.2. IL-4/IL-13R Inhibitors

Alamon et al. found that the use of IL-4/IL-13R Inhibitors-Dupilumab to control the disease was effective in patients with intractable HHD. Patients were followed up for 5 months and were found to be in significant remission with no new lesions<sup>11</sup>. The results indicate that Dupilumab may be beneficial for the treatment of HHD. According to the case report, the mechanism of Dupilumab's efficacy could be due to immunomodulatory and pruritic ameliorating effects.

## 5. Conclusions

HHD is a rare chronic dominant genetically inherited skin disease. The disease is relatively difficult to treat and has a significant impact on patients' quality of life. Because of the low prevalence of HHD, there are not sufficient patients to investigate. Currently, HHD treatment options are primarily based on case reports or case series. To define a standardized treatment protocol, large randomized controlled clinical trials in multicenter hospitals are necessary. Patients with HHD may be candidates for topical agents. Physicians can also establish personalized treatment plans based on the patient's condition.

## References

- [1] Hailey H. Familial benign chronic pemphigus; report thirteen years after first observation of a new entity. *South Med J*. 1953;46(8):763-765.
- [2] White F, Shvartsbeyn M, Meehan SA, Urbanek RW. Benign familial pemphigus (Hailey-Hailey disease). *Dermatol Online J*. 2015;21(12).
- [3] Martin L. [Hailey-Hailey disease]. *Ann Dermatol Venereol*. 2000;127(12):1114-1116.
- [4] Ben Lagha I, Ashack K, Khachemoune A. Hailey-Hailey Disease: An Update Review with a Focus on Treatment Data. *Am J Clin Dermatol*. 2020;21(1):49-68.
- [5] Rogner DF, Lammer J, Zink A, Hamm H. Darier and Hailey-Hailey disease: update 2021. *J Dtsch Dermatol Ges*. 2021;19(10):1478-1501.
- [6] Burge SM. Hailey-Hailey disease: the clinical features, response to treatment and prognosis. *Br J Dermatol*. 1992;126(3):275-282.
- [7] Langenberg A, Berger TG, Cardelli M, Rodman OG, Estes S, Barron DR. Genital benign chronic pemphigus (Hailey-Hailey disease) presenting as condylomas. *J Am Acad Dermatol*. 1992;26(6):951-955.
- [8] Pasmooij AMG. Topical Gentamicin for the Treatment of Genetic Skin Diseases. *J Invest Dermatol*. 2018;138(4):731-734.
- [9] Aoki T, Hashimoto H, Koseki S, Hozumi Y, Kondo S. 1alpha,24-dihydroxyvitamin D3 (tacalcitol) is effective against Hailey-Hailey disease both in vivo and in vitro. *Br J Dermatol*. 1998;139(5):897-901.
- [10] Farahnik B, Blattner CM, Mortazie MB, Perry BM, Lear W, Elston DM. Interventional treatments for Hailey-Hailey disease. *J Am Acad Dermatol*. 2017;76(3):551-558 e553.
- [11] Alamon-Reig F, Serra-Garcia L, Bosch-Amate X, Riquelme-Mc Loughlin C, Mascaro JM, Jr. Dupilumab in Hailey-Hailey disease: a case series. *J Eur Acad Dermatol Venereol*. 2022;36(10):e776-e779.