# Current and future treatment options for insect bite hypersensitivity

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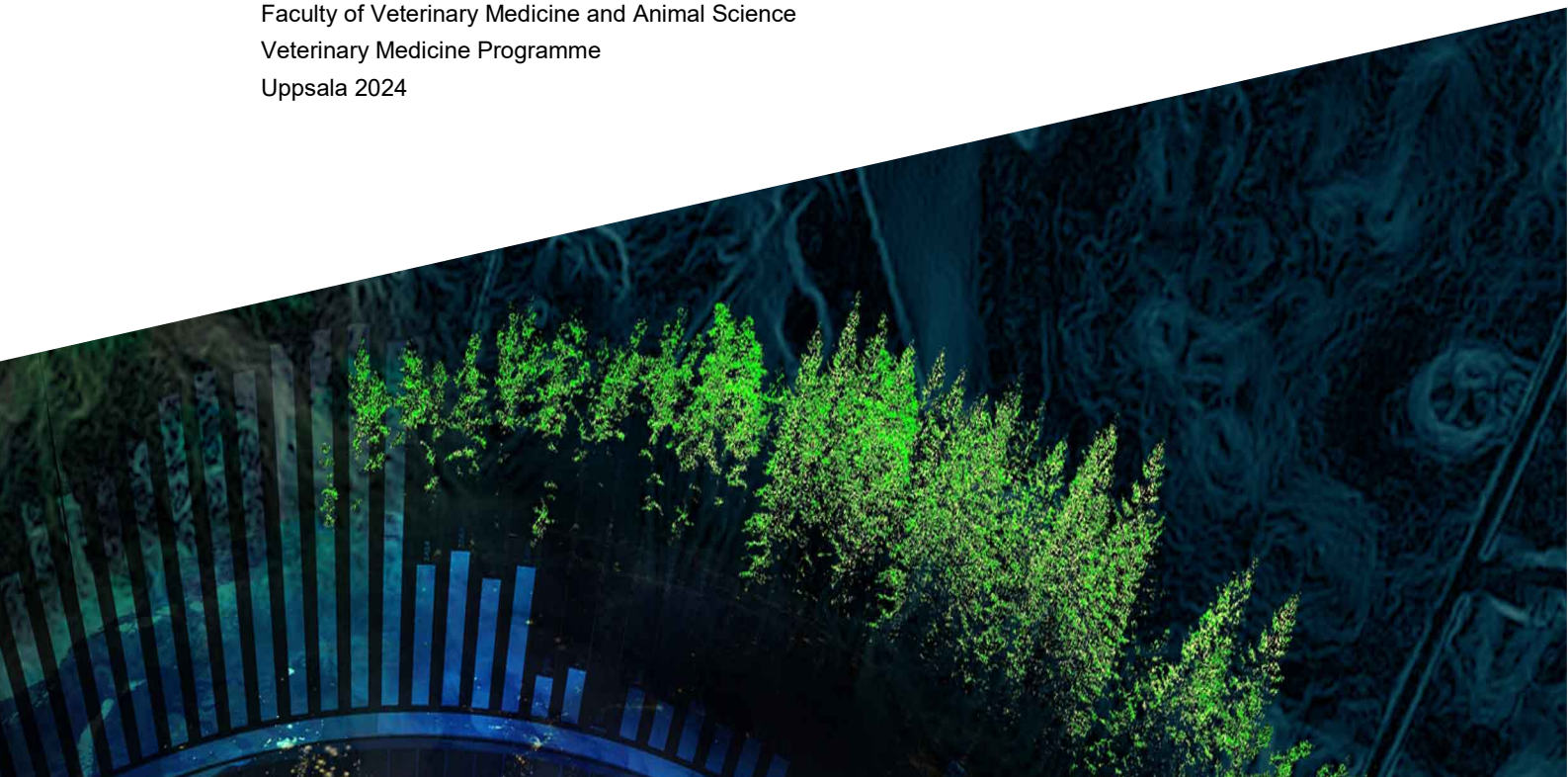

# Current and future treatment options for insect bite hypersensitivity

*Nutida och framtida behandlingsalternativ för sommareksem hos häst*

Selma Bergström

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## Abstract

This paper explored the treatment options available for insect bite hypersensitivity (IBH) in horses through a literature study. The conclusion was that drugs used today to treat IBH are primarily systemic glucocorticosteroids and antihistamines. However, antihistamines have not been proven effective enough by themselves, even when high plasma concentrations are achieved. Systemic glucocorticoids have a good effect on IBH but carry many severe adverse effects and other treatment alternatives are therefore warranted. Traditional treatment methods such as rugging and stalling horses inside, alongside the use of fans and insect repellants are often used. New drugs such as vaccines against IL-5 and IL-31 have shown great potential as possible treatments of IBH. These types of vaccines have shown good effect on pruritus in dogs. At the moment these vaccines are too expensive to produce for treatment of equines and therefore not commercially viable. To summarize, improved therapies that are cost efficient are needed to treat IBH in horses.

*Keywords:* Equine, Insect bite hypersensitivity, Antihistamines, IL-31, IL-5, Treatment, Therapies, Allergy, Pruritus

## Sammanfattning

Detta arbete har genom en litteraturstudie utforskat de olika behandlingsalternativen som finns tillgängliga för sommareksem hos häst. Slutsatsen som drogs var att de läkemedel som primärt används idag för att behandla sommareksem är glukokortikoider samt antihistaminer. Dock så har antihistaminer inte funnits vara tillräckligt effektiva även när höga plasmakoncentrationer har uppnåtts. Systemiska glukokortikoider har en god effekt på sommareksem men har risk för flera allvarliga bieffekter, det är således motiverat att ta fram andra behandlingsalternativ. Traditionell, konservativ behandling såsom att täcka och använda insektsmedel på hästarna, samt hålla hästar inomhus tillsammans med andra åtgärder för att hålla området insektsfritt används ofta för behandling. Nya läkemedel såsom vacciner mot IL-5 och IL-31 har visat stor potential som möjliga behandlingar för sommareksem. Dessa typer av vacciner används framgångsrikt för att behandla klåda hos hund, de är dock i dagsläget för dyra för att kunna producera för häst och är därmed inte kommersiellt gångbara. Sammanfattningsvis så krävs det nya förbättrade behandlingar som är kostnadseffektiva för att behandla sommareksem hos häst.

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# Abbreviations

| | |
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| IBH | Insect bite hypersensitivity |
| IgG | Immunoglobulin G |
| IL | Interleukin |
| Th2 | T helpercell 2 |

# 1. Introduction

The most common allergic skin disease of horses is insect bite hypersensitivity (IBH) which manifests clinically through chronic seasonal relapsing dermatitis (Littlewood 2013). The condition is caused by insect bites from the family Culicoides (Quinn et al. 1983; Fadok & Greiner 1990). Initially IBH presents as pruritic dermatosis which frequently affects the mane and tail area. This process is commonly followed by self-trauma such as biting and/or rubbing the affected areas which leads to hair loss and further irritation of the skin barrier. The trauma to the skin barrier significantly contributes to the development of secondary bacterial infections (Riek 1953; Kleider & Lees 1984; Broström et al. 1987).

Management of IBH includes minimizing the risk of bites by Culicoides. Common strategies are to make use of fly spray, fly blankets and/or keeping the horse inside to prevent bites. The clinical symptoms are often treated with systemic or topical corticosteroids often combined with systemic antihistamines (Cox & Stewart 2023). However, there are substantial side effects of the usage of systemic glucocorticoids in horses. Furthermore, the use of antihistamines can be questioned since they may not produce an efficient control of the symptoms (Olsén et al. 2011; R.S Cuming et al. 2016).

There is therefore a need for new treatments for IBH that have fewer side effects than glucocorticoids but still have a high efficiency. This thesis explores the current treatments available for IBH and if there is any potential in improving them, with the hypothesesis that horses need improved treatment of IBH and current treatments are not effective.

# 2. Methods

This literature study was performed between December 2023 and March 2024. The search engines used were Pub Med, Beva and Google Schoolar. The search words used were (horse OR equine) AND (insect bite hypersensitivity OR Culicoides hypersensitivity OR sweet itch OR dermatitis OR allergy OR pruritus). These have been combined with (treatment OR vaccine OR antihistamine OR glucocorticoids OR immunotherapy). Only published veterinary medicine studies and articles were used. For generic facts studylitterature has been used. For information on medicines, drugs and substances used in Sweden, the Swedish Physician Desk Reference (FASS) has been used.

**Limitations**
This thesis has only used articles written in Swedish or English. The literature had to be found in the web library and search engines of Swedish university of agricultural sciences.

# 3. Results

## 3.1 Etiology

IBH is a type 1 hypersensitivity reaction mediated by immunoglobulin E (IgE) (Wagner et al. 2006). In healthy horses' antibodies are produced against antigen without causing disease. Horses with type 1 hypersensitivity will produce more T helper cells type 2 (Th2) and produce a larger quantity of IgE-antibodies than healthy horses (Tizard, 2013). The most dominant response to the extracellular pathogens is the Th2 response. During a Th-2 response B cells are stimulated to produce allergen specific IgE, which will bind to the surface of mast cells and cross bind to the allergen. This process leads to degranulation of mast cells and the subsequent release of mediators such as histamine. These mediators start cascades which give rise to allergic symptoms (Tizard, 2013). The most important cytokines in type 1 hypersensitivity response are IL-4, IL-5 and IL-31 (Tizard, 2013).

## 3.2 Current treatment options

Treatment options available today are traditional treatment methods, these include rugs, insecticides and stalling horses to minimize the exposure to *Culicoides* midges. The clinical symptoms are often treated with systemic or topical corticosteroids that may be combined with systemic antihistamines. Trials of vaccines targeting IL-31 have recently been run, with promising results and these may prove to be a good treatment alternative in the future (Cox & Stewart 2023).

### 3.2.1 Traditional treatments

The management of IBH involves limiting the exposure to *Culicoides* midges as well as minimizing the pruritus to prevent secondary self-trauma. The only current method to eliminate signs of the disease is for the horse to reside in a *Culicoides*-free environment. To limit the exposure to *Culicoides* most horses are rugged and stable during dawn and dusk when the *Culicoides* are most active. Fans may also be used to clear the air from the midges. A chemical method to minimize exposure to *Culicoides* is the use of topical repellents (Cox & Stewart 2023).

### 3.2.2 Antihistamines

Antihistamines often work as antagonists on the H1-receptor, but some also exert other anti-inflammatory effects. First generation antihistamine is used as antiemetic and hypnoticum as they cross over the blood-brain barrier and therefore generate a

sedative effect. Exactly how antihistamine works is unclear today but through in vitro studies we have learnt that they decrease the histamine mediated smooth muscle contraction in bronchial tubes, intestines and uterus (Moe 2016). Antihistamines act as competitive antagonists for histamine receptors in tissues. In equine medicine H1 antagonists such as tripelennamine, promethazine and chloropheniramine have been used as treatment alternatives for IBH (Morrow et al. 1986) .

However, there is a need for more optimized antihistamine drugs that effectively treat horses with simple administration of the medication for owners to provide good compliance (e.g. oral), that have much less side effects then the other widely used substance (systemic corticosteroids). There are no such drugs approved for usage in animals in Sweden but there are several approved for man.

*Fexofenadine*

Fexofenadine is a selective non-sedating histamine H1 - receptor antagonist, which is clinically active in the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria in man. Fexofenadine is regarded as being safe, even at higher plasma concentrations in man (Olsén 2007). However, fexofenadine has been shown to have a low oral bioavailability in horses (Törneke et al. 2003).

*Cetirizine*

Cetirizine is a second-generation histamine H1 - antagonist, which is widely used in human medicine to treat seasonal/perennial allergic rhinitis and chronic idiopathic urticaria (Zuberbier & Henz 1999; Simons 2001). The pharmacokinetics of cetirizine in horses given a single oral dose of the drug has shown a favorable pharmacokinetic profile (Olsén 2007). In a study where six healthy standardbred trotter mares were given cetirizine in doses of 0.2-0.4 mg/kg per Os, it was proven that this dose reduced histamine-induced cutaneous wheal formation after a weeks treatment. The lower dosage (0,2mg/kg) gave a blood plasma concentration of 16 (± 4) ng/mL after 3 administrations with 12 hours interval. This dosage inhibited the development of histamine-induced cutaneous wheal formation to 45 % (± 23 %). The higher dose (0.4 mg/kg) gave after 4 more administrations with 12 hours interval a 3-fold higher blood plasma concentration (48 ± 15 ng/mL) and the development of histamine-induced cutaneous wheal formation were further reduced to 68 %± 11 % (Olsén et al. 2008).

Unfortunately, a larger study performed at a later stage could not find a significant difference between cetirizine treated horses and placebo horses. The study originally included 157 horses with signs of IBH under at least two seasons before entering the study. They were given the same doses as the previous study (0.4 mg/kg) and were monitored during the summer. The study was double blinded, and the horses were given 0.4 mg/kg body weight per Os two times a day during three weeks after they started showing signs of IBH. The horses underwent a clinical examination and blood tests were taken both before and after the treatment period and the range/severity of the symptoms were assessed by a veterinarian. The blood plasma concentration was measured to an average of 18ng/mL, i.e. significantly

lower concentrations were obtained in this study than that reported for the standard bred trotter mares (Olsén et al. 2011).

Reasons as to why the expected effect of cetirizine failed, could be because antihistamine lacks enough effect against itching, which is a major part of the problem of IBH. None of the studies reported any side effects (Nyman 2007).

### 3.2.3 Immunotherapy

Allergen-specific immunotherapy is the practice of administering gradually increasing quantities of an allergen extract to an allergic subject to ameliorate the symptoms associated with subsequent exposure to the causative allergen (WHO definition) . Allergen-specific immunotherapy is used in both human and small animal dermatology. In equine atopic dermatitis several open studies have shown encouraging results using whole-allergen extracts (Christine Loewenstein 2009). Few studies have been published on the efficacy of ASIT for horses with IBH and results using whole-body extracts of Culicoides spp. are contradictory (Ginel et al. 2014).

A placebo-controlled study led by Ginel et al published 2013 on ASIT as a treatment method of IBH found that there was no significant improvement of ASIT treatment in horses affected by IBH. The study was performed by assigning the horses into two groups, those treated with ASIT and those receiving placebo. Each group consisted of 10 horses, 5 mares and 5 stallions. Between groups the horses had a closely balanced clinical score. ASIT was here formulated using alum-precipitated, adsorbed allergens prepared by a commercial laboratory that performed serological tests. The treatment group received multiple ASIT with *C. nubeculosus* antigen and relevant ELISA-positive allergens. The allergens were prepared in three 10-fold dilution vials, with a maximal concentration of 1 $910^3$ mg/mL protein in vial 3, following the standard procedure recommended by the manufacturing laboratory. Increasing volumes from vials 1 and 2 were administered subcutaneously every week until vial two administration was finished (9th week). The horses then received injections every 3 weeks 4 times until reaching the maximal dose of allergen to be administered (0.8 mL from vial 3; 21st week). The rest of the treatment period the injections were administered monthly. To ensure blinding to owners and clinicians evaluating the horses the placebo group were dispensed solutions in identically labeled vials and in similar consistency as the ASIT groups. The horses were not stabled and to be able to extend the time of the clinical trial a 5% non-residual cypermethrin formulation was used weekly as a spray in both groups. No other treatment was allowed. The main distribution of lesions in the horses studied were dorsal involving the tail, rump, mane, dorsal midline and face. Distal extremities and the abdomen were rarely involved. Initial clinical scores for both groups were similar. At each re-evaluation, clinical scores improved progressively with a transient worsening at the third evaluation in September. The scores of both groups grossly overlapped during the year, with the differences between mean clinical scores always being less than 8 units. Four horses from the placebo group and three horses from the treatment group had to be stabled

during periods of time ranging from 1-3 weeks. The study concluded that mean clinical scores at each re-evaluation time point were not significantly different between groups and a similar number of horses from each group had to be stabled when the owners considered clinical signs as unacceptable. This study therefore concluded that by using commercially available extracts and tests, there was no significant clinical response to one year of ASIT in horses with IBH. Although both groups did show a similar reduction in clinical scores that was significant by the end of the study, the researchers concluded that this improvement was probably related to the use of the weekly insecticide. However, the immunotherapy was well tolerated in all horses and no adverse reactions were recorded. (Ginel et al. 2014).

### 3.2.4 Glucocorticoids

Extended corticosteroid treatments are often required in horses with conditions such as allergic dermatitis and hypersensitivity reactions (Divers 2017). Glucocorticoids bind to glucocorticoid receptors and work at the cellular level by interfering with or decreasing the expression of pro-inflammatory genes and proteins without decreasing certain selected anti-inflammatory proteins. Furthermore, glucocorticoids interfere with leukocyte adhesion, phagocytosis, and cellular respiratory burst. They also decrease humoral and cell-mediated immunity (Divers 2017).

The adverse effects of glucocorticoids are well known. The most serious adverse events include immunosuppression predisposing to bacterial or fungal infections, along with decreased wound healing and insulin-resistant laminitis. Other less severe effects include hyperglycemia, polyuria/polydipsia, muscle wasting and rarely gastric ulcers or hepatic lipidosis. Horses receiving glucocorticoids are known to have a decreased immune response to vaccines and infection. Confirmed dose response risks of laminitis in horses receiving corticosteroids have not been proven, however practitioners know that incidences of laminitis may occur during treatment. In particular horses affected by equine metabolic syndrome are likely predisposed to laminitis as an adverse event following glucocorticoid administration. Horses treated with glucocortiocoids for an extended time should have a tapering of the dose over time to prevent adrenal insufficiency syndrome. Other adverse effects linked to glucocorticoids are electrolyte imbalances, especially hypokalemia (Divers 2017).

## 3.3 New therapies

### 3.3.1 Vaccines

New trials have been made to try to alleviate IBH caused pruritus with vaccines against IL -31 and IL-5.

*IL-31 Vaccines*

One of IBH major symptoms is the prolonged itching which leads to self-trauma. Interleukin-31 (IL-31) is a mediator in allergic pruritus across species. A vaccine consisting of equine IL-31 (eIL-31) covalently coupled to a virus-like particle has been trialed in horses affected by chronic pruritus of unknown origin (CPUO) that could not be explained by IBH. In a study, four horses affected by year-round CPUO were vaccinated with the IL-31 vaccine. The clinical signs and pruritic behavior were then documented via an owner questionnaire pre and post vaccination as well as through photos. The horses were followed during several months after the vaccinations, there was inter-individual differences as of the length of the control as well as if the horses needed additional boosters of the vaccine after the study was concluded. For three of the CPUO horses, clinical samples were taken. For these horses, the levels of IL-31, thymic stromal lymphopoietin (TSLP) and monocyte chemoattractant protein 1 (MCP-1) were quantified from skin punch biopsies. It was found that IL-31, TSLP and MCP-1 levels were upregulated in pruritic, alopecic skin lesions compared to healthy skin of the same horse. Clinical signs and pruritic behavior improved in all four horses upon vaccination with eIL-31-CuMVTTvaccine. The vaccine was well tolerated without safety concerns throughout the study. The drawback of this small clinical study was that it did not include any control horses with a clinical arm given the standard treatment. Based on the outcome, it was concluded that Anti-IL-31 therapy might be applied as an allergen-independent treatment option for horses with CPUO overcoming the challenges of identifying the allergic trigger prior to treatment (Fettelschoss et al. 2021).

A similar vaccine is used and approved for dogs for treatment against itching coupled to allergic dermatitis and clinical symptoms of atopic dermatitis. This is a widely used and well accepted vaccine, and considered a good treatment alternative as it decreases symptoms significantly (Bachmann et al. 2018). Further, there are no safety concerns when given to dogs, indicating their potential for safety also in larger populations of other species. However, when introduced as a treatment for equines, pharmacovigilance studies would be needed to follow up potential species and breed specific adverse reactions.

*IL-5 Vaccines*

Studies of vaccines targeting IL-5 have also been performed. Interleukin- 5 is the cytokine responsible for the maturation of eosinophils in the bone marrow and the eosinophil release into the circulatory system in response to allogeneic antigens. This vaccine was developed to induce auto-antibodies to decrease the eosinophil production and dermal migration leading to a minimized tissue inflammation and damage (Fettelschoss-Gabriel et al. 2018). The vaccine has been studied in a double-blinded, placebo-controlled randomized study. Thirty were administered the vaccine or placebo monthly for three months with a fourth vaccination given again two months later. Blood samples were taken each month, and the clinical improvement was followed through; blood eosinophil counts and antibody titers, and parasite load were measured through fecal floats. Of the vaccinated horses, 47% had a 50% or greater reduction in clinical signs, whereas only 13% of the placebo

control horses had the same results. In 21% of vaccinated horses a 75% reduction of clinical signs were seen, which was not observed in any of the control horses. An increase in antibody titers against IL-5 were observed in 17/19 vaccinated horses (Fettelschoss-Gabriel et al. 2018).

A study published in 2020 with the aim of establishing a safety profile for virus-like particle-based vaccines targeting self-protein IL-5 in horses found that vaccination induces a strong B-cell and vaccine specific T cell response without the induction of IL-5 specific T cell responses. The study concluded that the vaccine is a safe therapeutic option for IBH-affected horses (Rhiner et al. 2022). However, a later study conducted with the aim of evaluating whether an equine anti-IL-5 vaccine affected blood basophil counts found that the basophil counts were unchanged after the first vaccination year, but a significant decrease in counts was evident after the second year. This study measured a decrease in basophil counts along with reduction in blood eosinophils as the clinical outcome of the vaccination over the course of 3 years. This study suggests a bystander effect of the anti-IL-5 vaccine on basophil counts (Rhiner et al. 2022). An article published in 2023 found that yearly vaccination against IL-5 could be used as a potential tool for treating the long-term clinical signs of IBH (Cox & Stewart 2023).

# 4. Discussion

The hypothesis that horses need improved treatment for IBH and that current treatments are not effective could not be rejected, as current treatment methods were found to be inadequate. The primary drugs used for IBH are systemic glucocorticosteroids and antihistamines.

I consider that the most important factors for drugs to become successful in the veterinary field is ease of administration and low cost of medication. Low-cost drug means that the drug itself cannot be too expensive, or if the drug is expensive, it has to have high efficiency and long-lasting effect. When developing drugs dose regimes need to be taken into account. Medications that need to be given more than once or twice a day for a long period of time are often not successful in practice due to compliance reasons. As owners give the medication the dose regimes need to be built so that the typical owner (a full-time working owner) can give the medication in conjunction with feeding and taking care of the horse. Hence, the target product profile (TPP) should be dosage given once or maximum twice daily. Further the drug should not be too sensitive to variations in time of administration, so that the owner or caregiver can give the medication with a couple hours difference without any major consequences. Another important factor is the route of administration. It is most common that the owner gives the animal the medication and therefore it should be possible to administer it by a non-medical trained person. An example of a drug which has become successful as of late is the drug Librela for arthritis in dogs. It is an injection given once a month, the injection is subcutaneous and can be given by both veterinary staff and trained animal owners. The alternative to this drug is often NSAID which, among other things, is cheaper but needs to be administered orally every day and has more side effects. This makes Librela a good candidate as the owners only need to give the medication once a month compared to every day, many owners therefore choose to give their dogs Librela despite the increased cost.

Unfortunately, antihistamines have not been proven effective enough by themselves, even when high plasma concentrations are achieved. Cetirizine is an antihistamine that has been proven to have a good oral uptake in equines and has shown good effect on reducing histamine-induced cutaneous wheal formation in a smaller study (Olsén et al. 2008). However, this was not possible to reproduce in a larger follow up study of horses affected by IBH. In a larger cohort no significant difference was observed in symptoms between horses treated with cetirizine or placebo. It was also noted that the horses in the larger study did not obtain the same plasma concentration as the horses in the smaller study despite being given the same dose (Olsén et al. 2011). This could also have an effect on the outcome of the study, reasons as to why the horses in the larger study had a lower plasma concentration could be because of breed and/or sex differences, as the first study only used standard bred trotter mares and the larger had different ages, sexes and breeds. Other factors for the lower plasma concentration could be that the owners giving

the medications may be less experienced than the researchers, resulting in missed doses or irregular doses or smaller doses. However, the horses did have a plasma count (18ng/ml) which had been proven effectful in the previous study. The reason it did not show any effect may be that the itch associated with IBH was so severe that cetirizine alone could not suppress it.

Systemic glucocorticoids have a good effect on IBH but carry many severe adverse effects that are wished to be avoided (Divers 2017). Often horses suffering from IBH are treated with glucocorticoids for a long period of time which increases the risk of adverse effects. More research is needed to understand the origin of the severe adverse reactions in equines. If the mechanisms are better understood there is a potential that glucocortiocoid treatments could be used better in the future. It is likely that the treatment can become more efficient and safer if there is a better understanding of how to individualize the treatment plan of glucocorticoids for the horse to be treated. Other current treatments are the more traditional non-therapeutic methods such as rugging and stalling horses inside, alongside the use of fans and insect repellants (Cox & Stewart 2023). It is difficult to keep horses in an insect free environment without negatively affecting animal welfare, which is why other medical options for these horses are so important.

New drugs on the treatment of IBH have been investigated out of which the vaccines against IL-5 and IL-31 hold great promise. These vaccines have yet only been studied in relatively small clinical studies. One study has found a correlation to lower basophil levels after vaccination, however the clinical relevance is unclear (Rhiner et al. 2022). Other studies published on the subject have not found any other side effects of note. Similar drugs are used in the treatment of atopic dermatitis and allergic dermatitis in dogs and have been shown to have a good effect on pruritus in dogs (Olomski et al. 2020). However, the main problem with the vaccines at the moment is the economical aspect, as they are expensive to produce and therefore not commercially viable (Cox & Stewart 2023). With the continued development of these vaccines as well as larger studies performed on them, hopefully the production cost can go down and therefore lead to a safe and viable treatment option. Future vaccines against IBH would probably be highly warranted and the owners have a relatively positive willingness to pay for this type of medicines. The reason for the latter is that this would enable the horses to roam freely in the fields and can be used for their intended purpose without the need for being stabled or treated for the self-trauma from itching.

Interesting treatment options for the future may therefore be the new trialed vaccines as they are efficient and similar vaccines are widely used within small animal and canine medicine with few side effects noted. Other interesting treatment options may be immunotherapy, ASIT, which is also widely used on canines with good effect (C. Loewenstein and R.S. Mueller 2009). However, studies of horses with IBH with the outcome of the treatment has been inconclusive till date (Ginel et al. 2014). More research is therefore needed to prove a positive effect of ASIT in horses with IBH.

There may also be an opportunity to continue the development and research on antihistamines such as cetrizine. It would be a great market and treatment as it is easy for owners to give to their horses and has few side effects. As of this paper it is not known why cetirizine underperformed in the larger study by Olsén et al. 2011 made with horses affected by IBH. Factors may include that the larger study used horses of different breeds affected by IBH and the smaller study used six healthy horses' trotter mares, there may be a difference in the hypersensitivity reaction or absorption of the drug both between breeds and healthy contra IBH affected horses which has not yet been explored.

The only treatment which has been proven effective is systemic or topical use of glucocorticoids as well as minimizing the horse's exposure to *Culicoides* midges. Which is unfortunate as this treatment has many adverse effects as well as imposes on the horse's welfare. The traditional treatment methods often include less time for the horse outside and decreases the horse's ability to express certain natural behaviors that have been shown to be important for the horse's wellness and welfare.

## 4.1 Conclusion

This thesis explored the hypothesis that current therapies to alleviate IBH are not effective and that horses need improved treatment of IBH, there was no support of that the null hypothesis could be rejected based on the literature study performed. The literature studies found that in particular vaccines are interesting to continue to develop for the treatment of IBH. At the moment they are too expensive but their efficiency and trialed dose regime of one injection a month is making it a promising alternative for owners. Of the available drugs on the market, cetirizine is an interesting compound to continue to explore. Cetirizine is a widely available drug and used on humans, making the drug cheap to produce and sell. It is given orally which means owners can easily treat their horses at home. For cetirizine the variable response to treatment in horses need to be better understood. If e.g. treatment predictive biomarkers can be identified, cetirizine may show promise in the treatment of specific horse cohorts.

# References


Bachmann, M.F., Zeltins, A., Kalnins, G., Balke, I., Fischer, N., Rostaher, A., Tars, K. & Favrot, C. (2018). Vaccination against IL-31 for the treatment of atopic dermatitis in dogs. *The Journal of Allergy and Clinical Immunology*, 142 (1), 279-281.e1. https://doi.org/10.1016/j.jaci.2017.12.994

Broström, H., Larsson, Å. & Troedsson, M. (1987). Allergic dermatitis (sweet itch) of Icelandic horses in Sweden: An epidemiological study. *Equine Veterinary Journal*, 19 (3), 229–236. https://doi.org/10.1111/j.2042-3306.1987.tb01389.x

Christine Loewenstein, R.S.M. (2009). *A review of allergen-specific immunotherapy in human and veterinary medicine - Loewenstein - 2009 - Veterinary Dermatology - Wiley Online Library*. https://onlinelibrary.wiley.com/doi/10.1111/j.1365-3164.2008.00727.x [2024-03-10]

Cox, A. & Stewart, A.J. (2023). Insect Bite Hypersensitivity in Horses: Causes, Diagnosis, Scoring and New Therapies. *Animals : an Open Access Journal from MDPI*, 13 (15), 2514. https://doi.org/10.3390/ani13152514

Divers, T.J. (2017). Use of Corticosteroids in Equine Practice. 2017
Fadok, V.A. & Greiner, E.C. (1990). Equine insect hypersensitivity: skin test and biopsy results correlated with clinical data. *Equine Veterinary Journal*, 22 (4), 236–240. https://doi.org/10.1111/j.2042-3306.1990.tb04259.x

Fettelschoss, V., Olomski, F., Birkmann, K., Kündig, T.M., Bergvall, K. & Fettelschoss-Gabriel, A. (2021). *Interleukin 31 and targeted vaccination in a case series of six horses with chronic pruritus - Fettelschoss - 2021 - Equine Veterinary Education - Wiley Online Library*. https://beva.onlinelibrary.wiley.com/doi/10.1111/eve.13408 [2024-01-11]

Fettelschoss-Gabriel, A., Fettelschoss, V., Thoms, F., Giese, C., Daniel, M., Olomski, F., Kamarachev, J., Birkmann, K., Bühler, M., Kummer, M., Zeltins, A., Marti, E., Kündig, T.M. & Bachmann, M.F. (2018). Treating insect-bite hypersensitivity in horses with active vaccination against IL-5. *Journal of Allergy and Clinical Immunology*, 142 (4), 1194-1205.e3. https://doi.org/10.1016/j.jaci.2018.01.041

Ginel, P.J., Hernández, E., Lucena, R., Blanco, B., Novales, M. & Mozos, E. (2014). Allergen-specific immunotherapy in horses with insect bite hypersensitivity: a double-blind, randomized, placebo-controlled study. *Veterinary Dermatology*, 25 (1), 29-e10. https://doi.org/10.1111/vde.12092

Kleider, N. & Lees, M.J. (1984). Culicoides Hypersensitivity in the Horse: 15 Cases in Southwestern British Columbia. *The Canadian Veterinary Journal*, 25 (1), 26–32

Littlewood, J.D. (2013). Clinical Manifestations of Culicoides Hypersensitivity. I: *Veterinary Allergy*. John Wiley & Sons, Ltd. 287–290. https://doi.org/10.1002/9781118738818.ch45

Moe, A. (2016). Sommareksem hos islandshäst. 2016

Morrow, A.N., Quinn, P.J. & Baker, K.P. (1986). Allergic Skin Reactions in the Horse: Response to Intradermal Challenge with Fractionated Culicoides. *Journal of Veterinary Medicine, Series B*, 33 (1–10), 508–517. https://doi.org/10.1111/j.14390450.1986.tb00062.x

Nyman, C. (2007). Behandling av sommareksem hos häst med cetirizin – ett fältförsök. 2007

Olomski, F., Fettelschoss, V., Jonsdottir, S., Birkmann, K., Thoms, F., Marti, E., Bachmann, M.F., Kündig, T.M. & Fettelschoss-Gabriel, A. (2020). Interleukin 31 in insect bite hypersensitivity—Alleviating clinical symptoms by active vaccination against itch. *Allergy*, 75 (4), 862–871. https://doi.org/10.1111/all.14145

Olsén, L. (2007). Drugs in Horses: Pharmacokinetics and Pharmacodynamics. 2007

Olsén, L., Bondesson, U., Broström, H., Olsson, U., Mazogi, B., Sundqvist, M., Tjälve, H. & Ingvast-Larsson, C. (2011). Pharmacokinetics and effects of cetirizine in horses with insect bite hypersensitivity. *The Veterinary Journal*, 187 (3), 347–351. https://doi.org/10.1016/j.tvjl.2009.12.030

Olsén, L., Bondesson, U., Broström, H., Tjälve, H. & Ingvast-Larsson, C. (2008). Cetirizine in horses: Pharmacokinetics and pharmacodynamics following repeated oral administration. *The Veterinary Journal*, 177 (2), 242–249. https://doi.org/10.1016/j.tvjl.2007.03.026

Quinn, P.J., Baker, K.P. & Morrow, A.N. (1983). Sweet itch: Responses of clinically normal and affected horses to intradermal challenge with extracts of biting insects. *Equine Veterinary Journal*, 15 (3), 266–272. https://doi.org/10.1111/j.2042-3306.1983.tb01788.x

Rhiner, T., Fettelschoss, V., Schoster, A., Birkmann, K. & Fettelschoss-Gabriel, A. (2022). Targeting eosinophils by active vaccination against interleukin-5 reduces basophil counts in horses with insect bite hypersensitivity in the 2nd year of vaccination. *The Veterinary Journal*, 288, 105896. https://doi.org/10.1016/j.tvjl.2022.105896

Riek, R.F. (1953). Studies on Allergic Dermatitis ("queensland Itch") of the Horse. *Australian Veterinary Journal*, 29 (7), 177–184. https://doi.org/10.1111/j.1751-0813.1953.tb13937.x

R.S Cuming, Groover, E.S., Wooldridge, A.A. & Caldwell, F.J. (2016). *Review of glucocorticoid therapy in horses. Part 1: Pharmacology - Cuming - 2018 - Equine Veterinary Education - Wiley Online Library*. https://beva.onlinelibrary.wiley.com/doi/abs/10.1111/eve.12555 [2024-01-11]

Simons, F.E. (2001). Prevention of acute urticaria in young children with atopic dermatitis. *The Journal of Allergy and Clinical Immunology*, 107 (4), 703–706. https://doi.org/10.1067/mai.2001.113866

Tizard, I. R. (2013). Type I Hypersensitivity. I: *Veterinary Immunology*. Ninth edition. St. Louis: Elsevier, 326-345.

Törneke, K., Ingvast-Larsson, C., Pettersson, K., Bergvall, K., Hedeland, M., Bondesson, U. & Broström, H. (2003). Pharmacokinetics and pharmacodynamics of clemastine in healthy horses. *Journal of Veterinary Pharmacology and Therapeutics*, 26 (2), 151–157. https://doi.org/10.1046/j.1365-2885.2003.00460.x

Wagner, B., Miller, W.H., Morgan, E.E., Hillegas, J.M., Erb, H.N., Leibold, W. & Antczak, D.F. (2006). IgE and IgG antibodies in skin allergy of the horse. *Veterinary Research*, 37 (6), 813–825. https://doi.org/10.1051/vetres:2006039

Zuberbier, T. & Henz, B.M. (1999). Use of cetirizine in dermatologic disorders. *Annals of Allergy, Asthma & Immunology: Official Publication of the American College of Allergy, Asthma, & Immunology*, 83 (5), 476–480. https://doi.org/10.1016/S1081-1206(10)62854-2

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