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Veterinary Dermatology

REVIEW

Equine allergic skin diseases: Clinical consensus guidelines of the World Association for Veterinary Dermatology

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Abstract

Background: Allergic skin diseases are common in horses worldwide. The most common causes are insect bites and environmental allergens.

Objectives: To review the current literature and provide consensus on pathogenesis, diagnosis, treatment and prevention.

Materials and Methods: The authors reviewed the literature up to November 2022. Results were presented at North America Veterinary Dermatology Forum (2021) and European Veterinary Dermatology Congress (2021). The report was available to member organisations of the World Association for Veterinary Dermatology for feedback.

Conclusions and Clinical Relevance: Insect bite hypersensitivity (IBH) is the best characterised allergic skin disease. An immunoglobulin (Ig)E response against *Culicoides* salivary antigens is widely documented. Genetics and environmental factors play important roles. Tests with high sensitivity and specificity are lacking, and diagnosis of IBH is based on clinical signs, seasonality and response to insect control. Eosinophils, interleukin (IL)-5 and IL-31 are explored as therapeutic targets. Presently, the most effective treatment is insect avoidance. Existing evidence does not support allergen-specific immunotherapy (ASIT) using commercially available extracts of *Culicoides*. Hypersensitivity to environmental allergens (atopic dermatitis) is the next most common allergy. A role for IgE is supported by serological investigation, skin test studies and positive response to ASIT. Prospective, controlled, randomised studies are limited, and treatment relies largely on glucocorticoids, antihistamines and ASIT based on retrospective studies. Foods are known triggers for urticaria, yet their role in pruritic dermatitis is unknown. Recurrent urticaria is common in horses, yet our understanding is limited and focussed on IgE and T-helper 2 cell response. Prospective, controlled studies on treatments for urticaria are lacking. Glucocorticoids and antihistamines are primary reported treatments.

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CLINICAL CONSENSUS GUIDELINES

Clinical Consensus Guidelines (CCGs) are intended to provide current information on the pathophysiology, diagnosis and treatment of dermatological conditions. The purpose of this consensus paper was to review the current literature and summarise the most up-to-date information available on equine allergic skin diseases in veterinary medicine. Literature was searched for publications using keywords such as equine allergic skin diseases, urticaria, food allergy, insect allergies, *Culicoides* hypersensitivity.

The statements are based on the best evidence that we have on this topic and, when no studies were available, recommendations are made based on expert opinion.

CULICOIDES HYPERSENSITIVITY

Introduction

Horses can be affected by a variety of allergic skin diseases. Insect bites are the most common triggers worldwide. Insect bite hypersensitivity (IBH) is the current name given to the allergic response of horses to the bites of blood-feeding insects; most frequently midge species belonging to genus *Culicoides (*Diptera: Ceratopogonidae) although in some cases black fly of the genus *Simulium (*Insecta: Diptera: Simuliidae*)* have been implicated.

Historical perspective

Insect bite hypersensitivity has a global distribution. Descriptions fitting the clinical manifestations of this disease have appeared in the veterinary literature for over 160 years. In the 1841, at the proceedings of the [British] Veterinary Medical Association, VMA Felix Delany presented a paper entitled 'On the skin of the horse, its functions and some of its diseases' in which he describes a disease 'Surfeit' that manifests as small 'papules on the skin with inflammation, deposition under the cuticle and peeling with loss of hair, which in some cases may progress to resemble mange'.[1] In discussions, several of the meeting participants reported that in their experience, 'Surfeit' was more common in the warmer months with a peak incidence in spring and autumn.

Further descriptions of skin conditions resembling IBH occur under the names prurigo[2] and pityriasis simplex.[3] Several early 20th Century papers describe a condition of horses resembling IBH referred to as 'sweet itch' in the UK[4] in which lesions begin as papules associated with severe itching leading to further traumatic injury to the skin, affecting the mane, tail and belly of the affected horses. The lesions are described as appearing in summer and disappearing in winter. Burk[3] also described the proliferation and scaling of the skin seen in prolonged cases of a condition he referred to as 'pityriasis simplex', which match clinical signs of chronic IBH: however, none of these early authors was able to provide a convincing explanation of the cause. It was not until 1891 that the first association with insect bites was made when Bancroft demonstrated that horses in Queensland were protected from 'Queensland Itch' if they were stabled from before dusk until after dawn.[5] Insect bites also were proposed as the cause of a similar condition referred to as 'summer sores' in German mine horses based on the observation that the condition disappeared when the affected animals were stabled underground.[6]

Attempts to define the cause of these conditions were hindered by the numbers of different names given to apparently similar skin diseases in differing parts of the world. In 1928, Allen and Kingstone[7] introduced the term 'lichen tropicus' to describe the condition seen commonly in India and previously referred to as prurigo by Haynes[2] or pityriasis simplex by Burk.[3] Interestingly, Allen and Kingstone[7] reported lichen tropicus to be more common in imported artillery horses (a situation reminiscent of the high prevalence of IBH in native Icelandic horses following export as adults into mainland Europe), and although they considered it likely to be an allergic reaction, this was ascribed to novel undigested food proteins caused by the change in diet. In 1934, the name 'Dhobie itch' was used by Underwood[8] to describe a condition of the skin of horses in the Philippines that he thought was associated with filarial larvae of *Habronema*, and the same author used the term summer sores.[9] In 1939, Datta then added to the confusion by renaming 'lichen tropicus' as 'microfilarial pityriasis' to signify his histological findings of filaria associated with the lesions.[10] The microfilarial hypothesis seemed attractive and could have explained the seasonal association with presence of biting insects; by this time, *Culicoides nubeculosus* was known to be the intermediate host of *Onchocerca cervicalis*[11] as were *Musca domestica* and *Stomoxys calcitrans* for *Habronema* spp.[12] Several cases of skin lesions in which microfilaria were present in deep skin scrapings also were reported from the United States.[13] Although some cases did have a similar distribution to IBH, localised granulomas were described in others.

The importance of filarial parasites was questioned on the grounds that the morphology of the parasite was different from typical *O. cervicalis* of the horse[7] and adult *Habronema* were seldom present in affected horses.[8] Neither author was able to explain why the filaria would only occur in some exposed horses, and Datta did consider that their presence may be coincidental, noting that the distribution of the lesions does not match the known location of *O. cervicalis* development in the ligamentum nuchae.[10] Increasing doubts about the filarial cause were supported by a French study of 'Dermatose estivale récidivante du cheval' (which was translated as summer sores) a name used in Normandy/France since at least 1840 for horses showing typical signs of IBH.[14] The authors did not detect any microfilaria in the lesions of the affected French horses yet did note a familial predisposition, and were the first to suggest heritability as an important factor. Likewise, Pires[15] in 1938 was unable to demonstrate *Habronema* larvae in lesions of

Brazilian horses suffering from a condition he referred to as 'Llaga de Verano', which also translates as summer sores. Taking a different approach, Pereira and De Mello exposed a healthy horse with no history of summer sores to repeated challenges with *H. muscae* larvae yet no lesions developed; by contrast, a donkey with a history of recurrent summer sores did develop lesions on first challenge with *H. muscae* larvae yet the effect reduced rapidly on subsequent challenges to the point where no reaction occurred. The authors concluded that filarial larvae could elicit a response and only in animals with some predisposing susceptibility.[16]

At least part of the controversy and mystery of what caused this pruritic skin disease in horses was eventually resolved by Riek who did not find microfilaria in Australian horses suffering from 'Queensland Itch'.[17] Building on the observations of Bancroft[5] that Queensland itch was associated with biting flies, Riek demonstrated positive allergic reactions to intradermal skin tests with *Culicoides robertsi* antigens, and went on to show that sensitivity could be transferred passively to the skin of unaffected horses by a heat labile serum antibody.[18]

With the benefit of hindsight, it would seem that much of the controversy was a consequence of misunderstanding the term 'summer sores', the meaning of which quite literally became 'lost in translation'. Some authors refer to a condition resembling IBH in which intensely pruritic lesions are distributed along the mane, withers, back and tailhead caused by an allergic reaction to insect bites (Insect Bite Hypersensitivity), while others use the term summer sores for a more localised granulomatous lesion frequently seen on the face and lips of horses associated with the larvae of *Habronema* spp. However, some truth may be found in both the allergic and microfilarial hypothesis. A recent case report from Romania describes a 22-year-old horse presented with pruritic mane and tail lesions matching those typical of IBH, in which *Onchocerca* larvae and marked eosinophil infiltration were detected in skin biopsies. The pruritus responded rapidly to ivermectin treatment, and the lesions healed in three weeks without further intervention, a course of events not consistent with typical IBH.[19]

Aetiology

The allergic nature and global distribution of IBH have been confirmed by numerous studies conducted in Europe, Asia and the Americas.[20–32] The consensus from this work shows that members of the genus *Culicoides* are the most relevant insect species in the aetiology of IBH, while the exact species of *Culicoides* varies in different geographical locations depending on which are locally abundant. Australian cases of Queensland itch were attributed to *C. robertsi*,[18] while in the UK the condition was initially attributed to *C. pulicaris*.[20] *Culicoides pulicaris* feeds predominantly along the dorsal aspects of horses where lesions of IBH are common, while the closely related species *C. punctatus* is found feeding on the ventral abdomen.

Although both *C. pulicaris and C. punctatus* are reported as biting horses throughout the UK, 90% of *Culicoides* spp. identified feeding on horses in Ireland consisted of *C. obsoletus* and the closely related *C. dewulfi*.[32] These species also were anecdotally thought to be feeding on horses in south-west UK (Douglas Wilson, unpublished observations) and similar *Culicoides* spp. have been reported feeding on horses from the Netherlands.[33]Several additional *Culicoides* spp. were found feeding on horses in smaller numbers[20] and a similarly diverse populations of locally abundant species of *Culicoides* were detected feeding on horses in New York State,[34] while *C. obsoletus* was most abundant in British Columbia, Canada[35] and *C. imicola* was considered the major species in Israel.[4] This pattern of diverse local species found on horses with a few dominant types accounting for 80%–90% of the bites is no doubt repeated in other parts of the world.

In addition to *Culicoides* (midges), *Simulium* (blackfly) Tabanidae (horse flies), Stomoxidae (stable flies), Culicidae (mosquitoes) and Phlebotominae (sandflies) are known to bite horses[36] and IgE antibodies to *Simulium*, Tabanidae and Culicidae proteins have been detected in the serum of horses exposed to their bites.[37–40]

Yet, not all the above insect species have been associated with IBH, and this probably reflects differences in their biology and abundance. For example, several species of Tabanidae are known to successfully feed on horses, yet in temperate regions, their season of activity is restricted to the warmest midsummer months. Horses also take action to limit the number of bites they receive, by tail-swishing, head-shaking, stamping and skin-twitching; they successfully dislodge the majority of tabanids shortly after they alight with only approximately 20% of feeding attempts resulting in a blood meal.[29] In addition, as tabanids prefer bright sunlight, horses will seek deep shade or shelter indoors when tabanids are abundant,[41–43] which further limits exposure. Where horses do show an inflammatory reaction to bites by Tabanidae, clinical signs are usually limited to a few discrete 1–2-cm-diameter swellings around the site of the bite; typically, younger horses are affected and the reaction subsides with time and exposure to more bites, although horses continue to react to the painful stimulus delivered by these large insects.

By contrast, *Culicoides* are active for much of the year with only a limited break during cold winter months or very dry seasons. Observations of horses confirm that during the dawn and dusk feeding periods they may be bitten by many hundreds if not thousands of *Culicoides*. The aggregation of all this activity will lead to a sustained antigenic challenge, which will inevitably result in extensive inflammatory lesions in those individuals that become hypersensitive to *Culicoides* antigens. Notwithstanding this, severe systemic illness or anaphylactic shock caused by *Culicoides* bites have not been reported.

Simulium can be present in very large numbers when the environmental conditions are favourable. There are several reports of severe attacks by *Simulium* resulting in systemic illness or even death of both

cattle and horses.[44–46] This has been attributed to shock caused by the presence of histamine in *Simulium* saliva,[47] yet this attribution does not stand up to scrutiny. The amount of histamine in each black fly's saliva is ≤3 ng per bite[48]; the numbers of bites reported at post mortem in cattle was 25–50,000, so a dose of 150 µg could have been administered, which is unlikely to be a fatal dose for an animal the size of a cow or horse. Thus, the cause of the severe reactions remains a matter of speculation; possibly, there are additional toxins found in *Simulium* saliva, or the reaction may be augmented by host mast cell degranulation either as an innate or an immunoglobulin (Ig)E-mediated response. As both passive transfer of antibodies to *Simulium* proteins or active immunisation with *Simulium* antigens has been shown to protect cattle from this type of severe reaction, an immune-mediated mechanism such as anaphylactic shock in sensitised animals (horses or cattle) could explain the aetiology of this condition.[11,47]

Feeding and salivary proteins

Female *Culicoides* require a blood meal to support egg production. Different *Culicoides* spp. have distinct hosts from which they feed and use sensors for carbon dioxide to detect the breath of animals and presumably other olfactory clues to identify their preferred host.[49] Those which feed on horses alight, crawl around and make their way down to the skin surface where they spend approximately 15-min feeding. The mouthparts consist of the epipharynx (labrum), maxilla (lacinia), mandible, hypopharynx and labium, with the overall length of the feeding apparatus measuring about 200 µm. Several of these keratinised structures have serrated edges at their tips and can be moved independently, acting as a saw which cuts into the skin; alternatively, they can interlock to form a conduit for the expulsion of saliva into the wound or ingestion of blood.[50] As is the case with all blood-feeding insects, a diverse range of salivary proteins are produced. In so-called 'pool feeders' such as *Culicoides*, these facilitate the formation of a pool of unclotted blood that can be ingested efficiently. Proteins that inhibit factor X, which hydrolyses prothrombin to thrombin during blood clotting, and apyrase, an enzyme that converts adenosine tri- to monophophatase (ATP to AMP), the former required for platelet aggregation, the latter a vasodilator, were the first factors to be identified.[51,52]

Digestive enzymes including hyaluronidase, trypsin and chymotrypsin[53,54] have been described and are likely to have a dual role: assisting the disruption of the skin and connective tissue during biting, and subsequently in digestion of the blood meal. Analysis of copy (c)DNA libraries derived from messenger (m) RNA of dissected salivary glands has provided a comprehensive range of secretory salivary gland proteins from *C. sonorensis* and *C. nubeculosus*[55]; many represent members of protein families such as the D7 pheromone-general odorant binding protein family, lectin, antigen-5-like proteins (Cul n 1) and Kunitz-like serine protease inhibitors, and several more have as yet known homologies or function.

Identification of allergens

Research aimed at identifying and synthesising recombinant versions of the *Culicoides* salivary proteins using data from cDNA libraries derived from *C. sonorensis* or *C. nubeculosus* has been carried out by several groups.[56–58] Initial analysis of potential allergens from *C. nubeculosus* using IgE-specific Western blotting and mass spectrometry identified maltase, hyaluronidase, members of the D7 family, several small basic proteins associated with blood feeding, and two proteins CnSG60 and CnSG79, 40–50 kD glycoproteins of unknown function.[56–58] A separate study using a cDNA library constructed with mRNA derived from *C. nubeculosus* salivary glands displayed on the surface of filamentous phages and enriched for clones binding serum IgE of IBH-affected horses confirmed these findings and added several additional putative allergens.[57]

Eleven putative allergens identified and expressed in *Escherichia coli* were shown to react with serum IgE from allergic horses, of which eight stimulated a reaction in intradermal tests. The identified allergens included some against which >40% of affected horses reacted, suggesting that a set of major allergens were present. These included Cul n 1 (a member of the known allergen family antigen 5), Cul n 2 (hyaluronidase), Cul n 4 (secretory protein of unknown function) and Cul n 3 and Cul n 5 (secretory proteins from the same 40–50 kD protein family as CnSG60 and CnSG79), confirming the importance of these allergens along with others to which only a few horses had antibodies.[58]

The evidence showing a greater sensitivity of horses to extracts of locally abundant wild-caught *Culicoides* spp. compared with the laboratory-bred *Culicoides*[22,59,60] prompted the development of recombinant antigens derived from the salivary gland sequence of *C. obsoletus* and *C. pulicaris*, which commonly feed on horses in Europe. In the first study, an IgE-binding enzyme-linked immunosorbent assay (ELISA) was used to assess several of the *C. nubeculosus* antigens previously described[54] and three new *C. obsoletus* allergens (Cul o 1, Cul o 2, Cul o 3) were identified. A diagnostic allergen-specific IgE ELISA against whole-body extracts was evaluated in a population of IBH-affected warmblood horses and compared to tests using recombinant allergens. Cul n 4, Cul o 2 (a D7 protein), Cul o 1 (a Kunitz protease inhibitor) provided the best combination of allergens as a diagnostic test.[61] A second study used seven new *C. obsoletus* recombinants identified as homologous to the known *C. nubeculosus* allergens. Again, in an IgE-binding ELISA, the *C. obsoletus* allergens proved to be more reactive than *C. nubeculosus* or *C. sonorensis*; moreover, versions of allergens expressed in baculoviral vectors were more potent that bacterial recombinants.[53,54,57]

Current research studies have used data from two cDNA libraries derived from either *C. obsoletus* or *C. pulicaris* salivary glands, and ion torrent sequencing of *Culicoides* salivary gland cDNA to derive a collection of >100 intact secretory protein sequences, which contain representative homologues of all previously identified allergens, as well as members of several abundant protein families not previously identified as allergens. The results of serum IgE binding highlight seven of the *C. obsoletus* and one *C. nubeculosus* antigens binding IgE from >70% of horses.[62] When IgE levels to 27 different recombinant allergens were determined in 199 allergic and 148 control horses, nine of those allergens were 'major allergens' and seven of those nine allergens were able to bind IgE in the sera from >70% of allergic horses. The authors concluded that combination of these top seven allergens could diagnose >90% of the IBH horses with a specificity >95%.

When IgE microarray profiling to 27 *Culicoides* r-allergens was conducted on 110 serological samples from Icelandic horses imported from Iceland to Switzerland, significant sensitisation was detected in the serum in the year of first clinical signs.[63] When a subset of these horses was tested the following summer, the increase in number of sensitisations and serum concentration of allergen-specific IgE was not statistically significant. Horses tended to become sensitised to multiple allergens rather than one single main allergen, consistent with true co-sensitisation rather than cross-reactivity. Of these allergens, nine were identified as major sensitising allergens that could be useful for preventative immunotherapy. In the same study, the authors examined the reactivity of sera from Icelandic horses that were not exposed to *Culicoides* and found some IgE reactivity, although usually at low IgE concentrations. The authors also examined the reactivity of Icelandic horses raised in Sweden and found that duration of IBH did not significantly affect the degree of sensitisation.

Lastly, a study compared IgE concentrations in sera of IBH-affected horses all living in a *Culicoides*-affected area and with different origins (i.e. born in Iceland vs. horses of the Icelandic breed and other breeds born in a *Culicoides*-infested area of Europe). This study revealed that Icelandic-born horses had higher serum IgE concentrations against the allergens and a higher area under the curve of rCul n 4 when compared to the European-born horses.[64]

Pathogenesis of IBH

As mentioned in the Historical perspective section, early studies indicated that IBH is caused by hypersensitivity reactions to *Culicoides* spp. First indications of the involvement of immediate type, most likely IgE-mediated hypersensitivity reactions, were provided using skin tests. Intradermal tests (IDT) with *Culicoides* extracts result in immediate type reactions followed by a late phase reaction up to 24-h postinjection. In some cases, reactions also were observed 48 h after the IDT,[22,59,60] suggesting that, in IBH cases, more than one type of hypersensitivity reaction might be involved. Indication of IgE involvement in the pathogenesis of IBH was provided with passive cutaneous anaphylaxis, where skin reactivity to *Culicoides* is transferred to normal horses with serum from affected animals.[65] The cell types and immune reactions shown to be important in the pathogenesis of IBH are reviewed below.

Keratinocytes and epithelial barrier

The epithelial barrier plays an important role in atopic dermatitis (AD) and the process of epicutaneous sensitisation in other species. Many horses with IBH also are atopic, yet relatively little is known about the potential disturbance of the epithelial barrier in IBH. In one recently published study, thymic stromal lymphopoietin (TSLP) was hypothesised to play a role as increased mRNA expression was demonstrated in lesional skin biopsies of IBH-affected horses compared with skin from healthy controls.[66] From that publication, it was not possible to determine whether IBH horses also were sensitised to environmental allergens and whether changes could be due to overlapping AD rather than being a signature of IBH.

Antigen presentation

Data on the role of antigen-presenting cells in IBH are scarce. Langerhans cells, identified as MHC II-positive cells with numerous Birbeck granules, were found to be increased in the developing lesions of IBH,[11] and also were located in the follicular epithelium and intradermal sweat ducts of IBH lesions.[67]

T lymphocytes

The involvement of T cells in the pathogenesis of IBH has been studied both in the skin and in the circulation; an imbalance of lymphocytic populations has been described towards a preponderance of T-helper 2 (Th2) cells. More specifically, skin biopsies of IBH lesions contain significantly higher numbers of CD4+ cells than CD8+ T cells.[68] The expression of mRNA associated with the Th2 cytokine interleukin (IL)-13, and not of IL-4 were significantly elevated in IBH lesional and nonlesional skin compared with skin from control horses.[68] This is in line with recent studies in humans, where IL-13 has been suggested to be the key Th2 cytokine driving inflammation in the peripheral tissues, while IL-4 has a more central effect.[69] IL-4 is thought to play a major role in the inflammatory reaction underlying human AD, while IL-13 is overexpressed locally and has a significant impact on the recruitment of inflammatory cells, contributing to alterations of the skin microbiome and to a decrease in the epidermal barrier function.[69] Furthermore, a decrease in the regulatory immune response in IBH skin is suggested by a lower mRNA expression of Forkhead box

P3 (FoxP3), a transcription factor of regulatory T cells (Tregs), both in lesional and nonlesional IBH skin compared with skin from control horses. The role of Tregs was not as clear at the protein level, as only horses with severe IBH lesions had a significantly lower ratio of Foxp3+ to CD4+ cells. No differences in expression of the Th1 cytokine gamma-interferon (γ-IFN) were found when comparing lesional, nonlesional and healthy skin biopsies.[68]

Skin biopsies taken after intradermal injections of *Culicoides* extracts revealed increased numbers of CD3+ lymphocytes in the dermis of IBH horses compared to sites injected with saline.[70] More recent studies showed an increased lymphocyte influx and IL-4 mRNA expression 24 h after injection of *Culicoides* whole-body extract in IBH horses compared with healthy controls. IFN-gamma mRNA was upregulated only in the skin of the healthy controls, and the authors concluded that this Th1 cytokine may be protective against *Culicoides* hypersensitivity. In that study, no upregulation of the mRNA Treg marker Foxp3 was observed.[71] The differences between the studies of Heimann[68] and Meulenbroeks[71] probably are a consequence of the fact that the former was performed on lesional skin biopsies while the latter was carried out with biopsies taken after intradermal injection. The advantage of biopsies taken after intradermal injection are that the time frame and injection site are controlled, which is not the case when biopsies from IBH lesional skin are taken. However, injection of crude *Culicoides* extracts, which contains hundreds of proteins irrelevant for IBH yet with immunostimulating capability, induces an immune response that will differ from a natural bite of *Culicoides* where only saliva is injected into the skin. This is likely to explain the differences found in 'natural' IBH skin lesions and in skin biopsies taken following intradermal injection. Nevertheless, all the studies discussed convincingly show an increased Th2 response in the skin of IBH-affected horses, while the local Th1 response is not influenced by the disease status or is even decreased in IBH compared with control horses.

An increased Th2 and decreased Th1 response also can be detected in the circulation of IBH horses after in vitro re-stimulation of peripheral blood mononuclear cells (PBMCs), both at the mRNA and protein concentrations.[72] Furthermore, decreased numbers of allergen-induced Tregs were demonstrated in IBH horses.[73] Functional studies showed that the suppressive capability of *Culicoides*-stimulated Tregs was significantly lower in IBH-affected compared with control horses and was associated with a significantly higher percentage of IL-4+ and a lower percentage of FoxP3+ IL-10+ T cells. These findings show the functional relevance of Tregs for tolerance to *Culicoides* saliva antigens in horses exposed to bites of these insects that do not develop IBH.[74]

Seasonal exposure to insect bites also seems to influence the immune response. Compared with summer, a significant decrease of IL-4 and increase of γ-IFN production was observed in winter in re-stimulated PBMCs from IBH-affected horses.[75] In skin biopsies, expression of Th1 and Th2 cytokines also was influenced by the season: mRNA expression of IL-4, IL-13 and γ-IFN was significantly higher during the IBH season than in the off-season. However, in that study, these changes were observed both in healthy and IBH-affected animals. The authors concluded that this general upregulation of cytokine expression during the IBH season probably is the result of an overall increased T-cell influx during the summer months, as it directly correlated with an increased CD3+ mRNA expression in the skin.[75] Reduced incidence of IBH was reported to be associated with a downregulation of IL-4 by IL-10 and TGF-beta, suggesting a role for these two cytokines in reducing the incidence of IBH.[76]

IgE and other antibody subclasses

Detection of allergen-specific IgE was impaired until monoclonal antibodies specific for equine IgE became available.[77] The first direct evidence of IgE involvement in IBH was documented by Wilson et al. showing binding of serum IgE from IBH horses to *Culicoides* antigens using immunohistochemical evaluation and later, IgE-binding to various *C. nubeculosus* salivary gland proteins using immunoblots.[39,78] Both studies demonstrated that *Culicoides* salivary gland antigens bind serum IgE from IBH-affected and not from control horses. Conversely, the sensitivity and specificity of an IgE ELISA using *C. nubeculosus* whole-body extract as antigen was rather low.[79] Interestingly, when whole-body extracts from *C. obsoletus*, the main *Culicoides* spp. in the environment of horses, or combinations of recombinant *Culicoides* allergens (r-*Culicoides* allergens) were used in IgE ELISA using monoclonal antibodies, the large majority of IBH-affected horses and only a few control animals showed IgE-binding to r-*Culicoides* allergens.[80,81] These findings were confirmed using a microarray with a panel of r-*Culicoides* allergens. This new technique has the advantage that many different allergens can be tested in the same run using only small amounts of serum.[65] Combination of a panel of these pure r-*Culicoides* allergens can result in IgE serological tests with high specificity and sensitivity for IBH diagnosis.[39,79–81] Such tests are not yet commercially available.

Horses have seven IgG subclasses with different effector function capabilities.[82] Which subclasses are associated with allergy has not yet been studied extensively, yet initial studies indicate that allergen-specific IgG5 and sometimes also IgG1 are increased in IBH-affected compared to control horses.[83] Interestingly, IgE antibodies are not useful as a predictor for the development of IBH as their increase occurs concurrently with the development of clinical signs, while the increase of IgG5 appears to precede the development of clinical disease.[83] Interestingly, when IgG antibodies were transferred from IBH horses to healthy horses, reactions similar to IBH lesions could be obtained with intradermal administration of *Culicoides* extracts.[83]

Basophils

Basophils are among the major effector cell population in allergy, infiltrating the site of the allergic reaction after

mast cell degranulation. Although present only in low concentrations in the blood, they are used to reproduce the allergic reaction in vitro: peripheral blood leukocytes (PBL) including the basophils are incubated with potential allergens for a short period of time (0.5–1 h). In allergic individuals, sensitised basophils degranulate following binding of cell surface-bound IgE with the specific allergen, then allergy mediators, typically histamine or leukotrienes, are released and are detected in the cell culture supernatant. Significantly higher histamine or sulfidoleukotriene release after stimulation of PBL with *Culicoides* allergens in IBH-affected horses compared with controls has been demonstrated.[18,26,84,85] When Icelandic horses were monitored in their development of IBH, sulfidoleukotriene release assays were unable to predict which horses would subsequently develop IBH.[86]

Mast cells and eosinophils

Insect bite hypersensitivity is characterised by a skin infiltration with mast cells and eosinophils.[11,22–88] Injection of *Culicoides* antigen into the skin leads to increased infiltration with eosinophils.[89] Increased numbers of tryptase-positive and IgE protein-positive mast cells as well as IgE mRNA-expressing cells, probably representing plasma cells, have been demonstrated in lesional IBH skin[90] supporting the role of IgE-mediated reactions in IBH.

Chronic allergen exposure leads to an increasing role for eosinophils. Blood eosinophil numbers correlate with IBH severity.[90] With chronicity, IgE appears to play a lesser role compared to eosinophils.[91] The eosinophil-driven delayed type hypersensitivity is characteristic of chronic IBH with accumulation of IL-5+ Th2 cells. Through a phenomenon called T-cell plasticity, a shift from conventional Th2 to pathogenic effector Th2 cells results in high levels of IL-5 cytokine production that promote eosinophil differentiation, migration, activation and survival.[92,93] It also is now accepted that in IBH horses, eosinophils are not only playing a role in late-phase Type I hypersensitivity and also in cell-mediated hypersensitivity (Type IVb).[23] Neutralisation of IL-5 through induction of IL-5 specific auto-antibodies reduced blood eosinophil numbers as well as the severity of IBH, supporting the important role that IL-5 plays in the pathogenesis of IBH.[90,94]

Pathogenesis of pruritus in IBH

Pruritus is a cardinal sign of IBH and much of the associated pathological changes are attributed to trauma subsequent to rubbing behaviour elicited by the pruritus. The sensory nerves, which mediate the sensation of itching, belong to a distinct population of unmyelinated polymodal C fibres with branched ends that terminate in the epidermis. They are activated by a diverse range of agonists that typically have multiple additional roles in inflammation and immunity.[95,195] Although pruritus-induced grooming behaviour plays an important adaptive role in reducing the burden of ectoparasites such as lice or ticks that live on the host,[97] it remains unclear how pruritus can be of benefit where it occurs as a consequence of an inflammatory reaction that is sustained long after the biting insect has gone. A further important consideration is the distinction between the transient sensations of itching, which are relieved by scratching, and the prolonged nonresolving pruritus that is a feature of allergic pathologies such as IBH and other chronic skin diseases. Current understanding of pruritus divides the condition into two subcategories based on whether the sensation is mediated by nerves activated by histamine or by non-histamine agonists.[95,96]

Histamine has the longest pedigree as a mediator of pruritus. Histamine acts by direct stimulation of H1 and H4 receptors expressed in sensory nerve endings causing an immediate itching response.[98] Histamine also acts as a neurotransmitter in the central nervous system, where through the H3 receptors, it has a role in regulation of sleep and cognitive functions, and in certain other peripheral nerves, particularly the enterochromaffin cells of the stomach, where histamine regulates gastric acid secretion through the H2 receptors. The most recently described H4 receptors are expressed in a wide variety of cells including lymphocytes, dendritic cells, mast cells, eosinophils and keratinocytes through which histamine exerts its actions as a key mediator of immune and inflammatory responses. Histamine is synthesised from the amino acid histidine by the enzyme histidine decarboxylase, yet the sources of histamine and the mechanisms by which it acts are still being elucidated. Histamine is present in all body tissues, largely stored in the form of granules in mast cells, from which it is released during inflammatory reactions, most notably in IgE-mediated hypersensitivity reactions such as IBH. During inflammatory or immune reactions, there is also de novo synthesis of histamine by histidine decarboxylase-expressing cells, particularly members of the macrophage/monocyte lineage, which contribute to the total histamine released. Within the skin, a further important source of nonmast cell histamine are the keratinocytes themselves, which express histidine decarboxylase in inflamed or chronically pruritic conditions, and not in normal healthy skin.[99,100]

Histamine is thought to have important roles in blood-feeding by insects. Histamine is present in the saliva of the pool-feeding *Simulium*,[36] where its presumed function in feeding is to cause vasodilation through its action on H1 receptors and further inflammatory reaction via H4 receptors on leucocytes and mast cells. By contrast, mosquitoes have a stealthier feeding behaviour using their long mouthparts to probe for a subcutaneous blood vessel, which often is not associated with itching at the time of the bite. Their saliva is proposed to have an anti-inflammatory action by binding histamine, 5-hyroxytryptamine, thromboxane and cysteinyl leukotrienes to the abundant D7 family of proteins found in their saliva[101]; however, mosquito bites can still induce pruritus in individuals that have developed a hypersensitivity. It is not known whether *Culicoides* saliva contains histamine, yet like *Simulium*, they too have a 'pool-feeding strategy' causing an erythema around the feeding site and *Culicoides* bites themselves are notoriously pruritic. D7 proteins, part of the large family of pheromone-binding sensory proteins, which bind small

volatile molecules, are abundant in both *Culicoides* and *Simulium* saliva yet their function or ability to bind histamine has not been tested. It is possible that mosquito D7 proteins may act to absorb inflammatory molecules and prevent itching, while D7 proteins from *Simulium* (or *Culicoides*) act as carrier molecules for the delivery of vasoactive amines during feeding, accounting for the immediate itching sensation reported by most individuals on being bitten. 5-hydroxytryptamine (5-HT) also stimulates sensory nerves via several different receptors; in low dosages, it elicits a sensation of itching and high concentrations 5-HT cause pain.[96] 5-HT is responsible for the severe pain caused by bites and stings from several arthropod species including bees and wasps, yet it is not known to be directly present in saliva of *Culicoides* or *Simulium*. Interestingly, expression of the gene coding for 5-HT receptor 3A was found to be upregulated in the epidermis of IBH-affected horses, indicating the presence of similar mechanisms in IBH.[66] Notwithstanding the potential for direct activation of sensory neurons by vasoactive amines in insect saliva, the major source of these mediators remains the mast cell. Both histamine and 5-HT are released from mast cells following allergen crosslinking of IgE bound to FcεRI on mast cell surfaces. Yet, it is of interest that antihistamines have been reported to provide the same efficacy as placebo in controlling clinical signs in IBH horses.[102]

Mast cell degranulation also releases proteolytic enzymes that stimulate nerves causing pruritus. This was first thought to be mediated by the G protein-coupled receptor PAR-2 (Protease activated receptor-2), in which cleavage of an N-terminal peptide by mast cell tryptase causes autoactivation of the receptor. Genetic knockout experiments showed that PAR-2 was not essential for the sensation of pruritus. However, the released PAR-2 terminal peptide SLIGRL does activate an additional receptor belonging to the Mas related G protein coupled receptor family (MRGPR), which caused the itching sensation.[96,103] Several members of the MRGPR receptor family are present on sensory nerves, which respond to peptide agonists. Both endogenous and exogenous proteases are known to generate peptide agonists that activate MRGPR and cause itch. There are several candidate proteases in *Culicoides* saliva, which may act to generate the peptide agonists and thereby contribute to an immediate itching sensation at the time of the bite irrespective of there being an allergic reaction.

Receptors for several cytokines produced by lymphocytes and other inflammatory cells have been identified on nociceptor nerves in skin. The list includes receptors for keratinocyte-derived TSLP, along with IL-33 receptors which have been reported to directly stimulate itching or to play a role in chronic itch. Additionally, IL-33 promotes the differentiation of Th2 lymphocytes that in turn secrete IL-31, IL-4 and IL-13 that also can activate receptors found on subpopulations of nerves in skin. Not all of these cytokines cause a direct sensation of itching when injected into skin and their actions are important for the development of chronic pruritus in a number of skin pathologies. IL-31 also plays a major role in pruritus development in IBH. IL-31 mRNA expression was found to be increased in lesional IBH skin, and expression of both IL-31 receptor subunits were upregulated in nonlesional epidermis of IBH horses.[104] These findings are further supported by the fact that targeting IL-31 significantly ameliorates clinical signs of IBH.[104] These cytokines signal through different pathways that converge around Ca++ influx through transient receptor potential cation channel subfamily V1 (TRPV1) and/or TRPA1. The understanding of these mechanisms using human disease and murine models has been rapid over recent years yet their role in pruritus associated with IBH remains largely speculative. Nevertheless, they provide a new route to the development of better drugs to treat pruritus and highlight the striking overlap between the mediators of pruritus and the immune regulation of Th2 lymphocytes, IgE antibodies, and the function of mast cells in the induction, and maintenance of allergic conditions such as IBH.

Consensus statement on pathogenesis in IBH

- A role for IgE, the conventional Th2 response, and the effector Th2 response promoting eosinophils is documented and accepted in the pathogenesis of IBH with IL-4, IL-13, IL-5 and IL-31 being identified as target for therapeutic intervention
- A skewed lymphocytic response with increased Th2 and decreased Tregs exists in IBH horses
- Th1 response is considered protective against IBH
- Currently, nine *Culicoides* antigens have been identified as 'major allergens' in IBH horses through studies focusing on IgE binding from sera of affected horses
- Standardisation of nomenclature is essential to avoid confusion
- Future large-scale studies are needed to define more precisely which allergens are important in different geographical locations
- Insufficient information is available to draw conclusions on the role of skin barrier dysfunction in the pathogenesis of IBH

Risk factors associated with the development of clinical disease

Insect bite hypersensitivity is a multifactorial disease resulting from a combination of genetic and environmental factors. Besides exposure to insects, environmental factors described to aggravate clinical sign of IBH included grazing outside and sunlight.[105] Other environmental conditions that were reported to play a role are habitats having soils of clay with heather and woody vegetation, while colder weather locations had a lower incidence of IBH.[30] Climate, rain fall, vegetation, stabling, type of bedding and deworming frequency also have been considered as factors that may play a role in IBH.[30,106]

The incidence of IBH varies in different parts of the world. It has been reported to range from 2.8% to 11.6% in the UK,[107,108] 21.8% in Israel[4] and ≤60% in Australia.[108] The age at which the animal is exposed for the first time to *Culicoides* is critical. Exposure later in life predisposes horses to the development of IBH. This has been well-documented with Icelandic horses that are introduced to *Culicoides* later in life and are at much higher risk for the development of IBH (>50%) than if they had had exposure to those insects early in life (approximately 5%).[109,110]

Older Icelandic horses exported to Central Europe developed IBH quicker than younger animals. Horses exported from Iceland and exposed to *Culicoides* before seven months of age had the same low risk of disease as if they had been born in Central Europe.[111] Export to Europe after seven months significantly increased the risk for development of IBH.

Sex and colour of the horse was not found to play a role in epidemiological studies on Icelandic horses in Norway[112] and in Israel.[113] The predisposition toward IBH is recognised to be genetically inherited.[114–116] Heritability was reported to be 0.08 in the Dutch Shetland pony.[117] Heritability also was demonstrated in Belgian warmblood horses with a heritability estimated in the range 0.65–0.78 using threshold animal models.[118] Higher ELA class II and/or overall inbreeding (pedigree or genomic) in Old Kladruber horses was associated with increased prevalence of IBH.[119] No single-nucleotide polymorphism (SNP) was identified although several regions of interest warrant further investigation.[120] The SNP-based analysis showed a highly significant association between the MHC region on ECA20 and IBH in Friesian horses.[121] Homozygosity across the entire MHC class II region was reported to be associated with a higher risk of developing IBH in two other distinct horse breeds.[122] A genome-wide association study aiming to identify and validate SNPs associated with IBH susceptibility reported novel associated loci on chromosome 1 and confirmed the polygenetic nature of IBH.[123] Mares were reported to have an additive impact on the development of IBH besides genetics, possibly as result of being part of the rearing environment.[124]

Consensus statement about risk factors for clinical development of IBH

- IBH is multifactorial disease resulting from a combination of environmental and genetic factors
- Warm humid climates with heavy exposure to *Culicoides* and close proximity to water increase the risk for development of IBH in predisposed horses
- Lack of exposure to *Culicoides* in the early stages of life significantly increases the risk for development of clinical disease
- Heritability varies among breeds yet it is widely accepted that predisposition for IBH is genetically inherited as a polygenetic disease.

Clinical signs of IBH

Age of onset of the disease can be at a young age, depending on the climate and insect exposure. In warm climates, clinical signs can occur in horses as young as two years of age[125] and are typically progressive over time so that each season the disease increases in clinical severity.[126] The clinical signs of IBH initially occur in the warmer seasons and go into remission during the winter months shadowing the populations of biting insects, thereby providing the basis for alternative names such as summer itch or seasonal dermatitis. In warm tropical areas, clinical signs may be nonseasonal.

Affected areas can be dorsal, ventral or both, depending on the feeding habits of the *Culicoides* spp. Specific to the geographical area.[127] Body regions classically affected are the ears, face, chest, legs, withers, rump, tail base, inguinal area and ventral midline.[128] The primary lesions are typically pruritic papules and/or wheals. Many horses develop secondary bacterial infections, which add to the degree of pruritus and complicate the clinical presentation.[129] Lesions of bacterial folliculitis present with inflamed circular areas of crusts and alopecia.

Pruritus can be extreme and leads to severe self-trauma and hyperaesthesia. It is accepted that IBH can be one of the most intensely pruritic diseases in horses. Affected horses commonly have broken hairs on their mane and tail, and excoriations on their rump, sides, chest and dorsal neck. Chronic and recurrent lesions are characterised by extensive alopecia, crusting and lichenification. Severe cases may lose all the hair from the mane and proximal third of the tail as a result of self- trauma. Chronically affected horses can develop rugal folds, leucodermac and leucotrichia. The distribution of lesions overlaps with cutaneous Onchocerciasis as this parasite is transmitted by *Culicoides*.

Some horses with IBH may develop hard calcified nodules consistent with eosinophilic granuloma.[130,131] These nodules may or not be pruritic. These areas of calcification are in most cases permanent. Although insects are not the only cause for the formation of equine eosinophilic granulomas, they are considered the most common cause of their development.[131,132] Some horses develop hives in conjunction with the pruritic dermatosis classic of IBH and thus insects should be considered when evaluating horses presenting for urticaria.[128,129]

Several studies have reported an association of IBH with respiratory disease.[81,133,134] The exact link between hyper-reactive airways and IBH is unclear. In a retrospective study using sera from IBH horses, horses with severe asthma or both the association between IBH and asthma does not seem to be linked to IgE-mediated immune reactions.[134] It is possible that the described clinical association may be a consequence of the fact that many IBH horses are atopic and may manifest their atopic trait with both skin and respiratory disease.

Consensus statement on clinical signs of IBH

- IBH is an extremely pruritic disease
- Distribution of signs often reflects the feeding sites of the *Culicoides* species present in the geographical region and can be dorsal, ventral or a combination of both. Sites commonly affected are face, ears, mane, tail, chest, ventral abdomen, and legs.
- Pruritic papular eruptions, hives, eosinophilic granulomas and hyperreactive airways can be seen in horses with IBH
- Secondary infections are common and significantly contribute to the level of pruritus

Diagnosis of IBH

Much effort has been placed on the identification of an accurate test to diagnose IBH, yet in practice it is still considered largely a clinical diagnosis that is made based on suggestive history, consistent clinical signs, exclusion of other pruritic diseases, and a positive response to insect avoidance either through physical barriers or by use of insect repellents. It is crucial to recognise and appropriately treat the secondary infections to enable assessment of the remaining underlying primary disease. Insect bite hypersensitivity also is frequently associated with other hypersensitivities, and it is not unusual to have IBH horses with concurrent environmental allergies.

Identification of allergen-specific IgE, whether by intradermal skin testing or serological testing, currently still is considered to be a minor criterion for the diagnosis of IBH. Positive results may be seen in clinically normal horses and may not be found in horses that are clinically compatible with IBH.[135] Thus the detection of allergen-specific IgE needs to be interpreted in the context of the clinical signs and history.

The duration of assessment of intradermal skin testing reactions in IBH horses has varied in various studies.[135,136] In one study, reactions were assessed at 30 min, 1, 4 and 24 h.[135] The reaction elicited by *Culicoides* extract in IBH horses was significantly larger than in normal horses at all time points using a concentration of 1/1000 w/v, and thus the authors concluded that this dilution was ideal for testing. Proposed dilutions of 1/50,000 w/v or 1/25,000 w/v of *C. variipennis (reclassified as C. sonorensis)* were reported for horses with seasonal dermatitis compatible with IBH.[135] It is of note that 28 of 38 clinically normal horses were found to be 'positive' 4 h after the allergen injection even using these dilutions.

Good agreement between intradermal skin testing and serological testing was found in a population of Malopolski horses diagnosed with IBH when allergen-specific IgE was measured using a monoclonal anti-IgE antibody.[136] Recently, much effort also has been put in the development of protein microarrays containing complex extracts as well as recombinant allergens. This type of technique allows the generation of mathematical models to calculate individual risk profiles, yet it is currently used only in research settings and not available in clinical practice.[137]

Skin biopsies also are not diagnostic for IBH as the findings are consistent with an allergic disease and not pathognomonic for IBH. On histopathological evaluation, IBH lesions are characterised by subepidermal oedema, acanthosis, para- and hyperkeratosis, and rete ridges, superficial and deep perivascular dermatitis with infiltration of eosinophils, lymphocytes, and mast cells.[23,72,73] Chronic lesions are characterised by a lymphohistiocytic perivascular infiltration without eosinophils.[23,72,73]

Consensus statement about diagnosis of IBH

- IBH is a clinical diagnosis based on compatible history, clinical signs, exclusion of other pruritic skin diseases and favourable response to insect control measures
- Positive allergen-specific IgE test results (whether based on serological or intradermal testing) are considered minor criteria and best used to support a clinically established diagnosis

Treatment

General considerations

In one study in which interviews were conducted with horse owners and veterinarians to obtain opinions on the value of various treatment strategies, it was clear that awareness of IBH was generally high. Owners commented on the impact of this condition on daily routines and the associated cost implications.[138] Most owners followed a multimodal approach that included a combination of physical barriers, chemical repellents and various supplements.[138]

Many treatments have been considered to provide relief to affected horses, ranging from oral to topical options. Currently, the most effective treatment strategy still relies on insect avoidance. However, minimising insect bites in real-life situations proves to be challenging. *Culicoides* are not strong flyers upwind (not being able to navigate flight at wind speeds over 6 mph) and typically do not fly long distances unless flying downwind.[139–143] They are most numerous in proximity to standing water.[148] Moving affected horses furthest away from bodies of standing water, stabling IBH horses at night (when *Culicoides* are most active), and the use of fans when stabled have been advocated to reduce insect bites.[142–144] These strategies are frequently difficult to implement as in warm climates, the evenings are the times when horses are typically turned out. Additionally, owners may have difficulty complying with changes in routine and husbandry.

The use of repellents is advocated yet much confusion and misinformation exist among owners and practitioners about what is an effective repellent. Additionally, in climates with high humidity and frequent rains, these products need to be reapplied more frequently than what is advertised on the labels, so many horses end up receiving insufficient protection from insect bites.

The use of physical protection, such as fly sheets and fly masks, also can prove to be challenging in hot climates with high ambient humidity. Sweating and trapping moisture under fly sheets and masks can turn into an additional risk factor for the development of secondary skin infection. Thus, there is need for effective, sustainable, safe treatments for affected horses. Frequently, in clinical practice, this involves the use of systemic glucocorticoids. Depending on the duration of the season and the severity of infections, these treatments may not be sustainable or even effective.

It is of note that when searching the literature on any randomised controlled study to evaluate the efficacy of systemic glucocorticoids (e.g. dexamethasone or prednisolone) for IBH, no prospective controlled study could be found. All of the published reports in the literature on the use of glucocorticoids for equine allergic skin disease are retrospective in nature and uncontrolled. See subheading on glucocorticoids for AD (Page 27).

Alternatives to glucocorticoids (e.g. antihistamines, fatty acid supplementations) have been considered yet, to date, the vast majority of these treatments have been evaluated in small studies which were not replicated, and thus no evidence-based conclusions can be made on their efficacy.

1. Fly sprays

Permethrin is a frequent ingredient of fly sprays. A pour-on topical 3.6% permethrin was evaluated for its repellent activity in seven pairs of horses in a controlled fashion.[145] Results showed a statistically non-significant reduction in the number of *Culicoides* that had taken a blood meal.[145] Owing to the small number of horses used in this study, the lack of statistical significance should not be extrapolated to a lack of clinical relevance. It is important, however, to consider that pour-ons take longer to distribute across the body and the mentioned study evaluated responses only after 24 and 48 h, not allowing sufficient time for the product to distribute especially onto typical feeding sites like the abdomen when applied over the dorsum. Also, the tents used for evaluation were placed within 1 m of each other and it is possible that the permethrin odours placed on a treated horse may have travelled more than 1 m, possibly deterring *Culicoides* in the untreated tent, and thus resulting in an equal reduction of *Culicoides*. Thus, maybe the issue was more about using the pour-on product rather than the ingredient per se. It is of relevance that another study showed that every other week application of 2% permethrin spray (Knockout LA) significantly reduced clinical signs in IBH horses.[146]

Ineffectiveness of 1% deltamethrin on the feeding of *Culicoides* has been documented in one study.[147] The efficacy of using nets, fans and repellents (DEET based) was assessed in a study in Switzerland, and the authors reported that there was no difference in efficacy between fans and nets, and that both strategies helped in decreasing the exposure to *Culicoides*.[148] The DEET-based product used in the Swiss study was selected as previously it had been shown to be effective.[149] More specifically, DEET (15%) had been demonstrated to be an effective repellent (with an average duration of 6 h) while citronella (0.6%) and cypermethrin (0.3%) were shown to be ineffective.[149]

Several products on the market in the USA contain cypermethrin at 0.15% (Tritec-14, Endure). The efficacy of a product containing a higher percentage of cypermethrin (1%, Ectomethrin H20 Equine fly spray) has not been evaluated in a controlled fashion. In one study that examined the repellent activity of various products sprayed on nets in a stable where horses functioned as the main source for attraction of *C. imicola*, it was reported that Tritec-14 (which is labelled to be effective for 14 days) had a greater ability to repel *Culicoides* than the control product for 2 h. In the same study permethrin (0.6%) was not shown to be effective.[150]

Citronella and lemon eucalyptus oil were assessed for their ability to repel *Culicoides* in a South African study. This combination was not effective and would, under certain conditions, even attract *Culicoides*.[151]

2. Topical options for pruritus and inflammation

In a double-blinded, placebo-controlled, randomised, cross-over clinical trial, 20 horses diagnosed with IBH were allocated to be treated daily either with an herbal spray (camphor, lemongrass, may chang, peppermint and patchouli) or a placebo for 28 days.[150] The treatment groups were crossed-over after a wash-out period of ≥28 days. Owners reported improvement of pruritus in 19 of 20 horses (95%) with complete resolution in 17 horses (85%) following treatment. Essential oil extracts from plants have been claimed to have anti-inflammatory, antipruritic and repellent activities, and for these reasons this strategy could be beneficial in allergic horses.[152,153,154] Compared with baseline, veterinarian-assessed scores of all individual parameters as well as the total sum of all scores were significantly different ($p < 0.05$) for the treatment group and did not reach significance for the placebo. The authors concluded that the beneficial effect was most likely the result of a summation of effects of the various ingredients.

In another study, a cream containing omega-3-fatty acids, humectants and emollients was evaluated in a study in which IBH horses were allocated to receive the placebo on one half and active ingredient on the other half of the body so that each horse was its own control.[155] Skin lesions on the treated side improved significantly between days 0 and 28 ($p < 0.0001$) in comparison to the untreated side. Antipruritic effects were not prominent and five of 28 horses showed adverse effects.

The effect of a topical phytogenic ointment on the healing of cutaneous lesions was investigated in a double-blinded trial involving 26 horses with IBH.[156] This

placebo-controlled trial lasted 21 days and reduction of lesions was reported in both groups; owners scored the level of comfort to be higher in the active ingredient group compared to the placebo group. Topical glucocorticoids such as topical formulations of triamcinolone and hydrocortisone are used in clinical practice to provide relief of clinical signs in selected areas although their efficacy has not been evaluated in randomised, controlled studies.[129]

3. Oral supplements

Various supplements have been considered to provide relief to IBH horses. High doses of n-3 fatty acids were evaluated in a randomised, double-blinded, crossover study.[157] The source of n-3 was linseed oil, and the source of n-6 was corn oil. The trial lasted six weeks and no significant effect on pruritus and lesions was reported, although most owners reported some level of improvement. Interestingly, flaxseed supplementation was able to reduce the lesional area of the skin test response of atopic horses.[158] The source of n-3 fatty supplementation is important and it has been shown that supplements derived from algae and fish oil are better incorporated in the blood and muscles of horses than flaxseed-derived supplements.[159] A supplement containing sunflower oil, vitamins, amino acids and peptides was evaluated in a placebo-controlled, double-blinded study with 50 IBH horses.[160] Half of them received the supplement and 25 received placebo for 30 days; thereafter all horses received the supplement for a further 30 days. The investigators scored the severity of IBH in all horses and owners scored the severity of the disease at the beginning of the study, after the first and second 30 day period. Investigators reported worsening of signs in the placebo group while owners did not detect a difference between placebo and active ingredient.

4. Antihistamines

Although antihistamines are frequently prescribed in clinical practice for the relief of clinical signs in IBH horses, very few studies are available and typically limited relief is seen in clinical setting, possibly owing to the fact that IBH is not just a histamine-mediated disease[93] and that histamine does not appear to be a major mediator of pruritus in horses. One placebo-controlled clinical trial evaluated the effect of cetirizine (at 0.4 mg/kg twice daily per os for three weeks) and reported no significant effect compared to the placebo.[102] In another study, chlorphenamine inhibited oedema and the accumulation of eosinophils and neutrophils in the skin of IBH horses injected with *Culicoides* allergens as evaluated by histopathological evaluation yet the clinical response in IBH was not assessed.[161] Therefore, the efficacy of antihistamines in the treatment of IBH horses may be dependent on the timing of administration in the course of disease along with the severity of disease.

5. Systemic glucocorticoids

No prospective, randomised controlled studies have been done to evaluate the efficacy of systemic glucocorticoids in IBH horses although they are one of the most commonly prescribed treatment in clinical practice. Prednisolone and dexamethasone are the most commonly used options.[129] Oral prednisolone is frequently prescribed at an induction dose of 1.5-2 mg/kg q 24 hr for 7–10 days and then tapered to 0.5 mg/kg q 48 hr. If prednisolone is not effective dexamethasone can be tried at 0.02–0.1 mg/kg q 24 hrs. Long term administration of glucocorticoids as the sole treatment for IBH is not recommended. See Page 27 for a detailed description of glucocorticoids in equine allergic skin diseases.

Consensus statement on the treatment of clinical signs of IBH

- Large, controlled studies are needed to make evidence-based recommendations on the treatment of IBH.
- Use of insect repellents and other means of insect avoidance largely remains the most effective long-term approach for treatment of IBH in clinical practice.
- Current evidence does not support the use of antihistamines as a monotherapy in any clinical phases of IBH.

ALLERGEN-SPECIFIC IMMUNOTHERAPY FOR THE TREATMENT OF IBH

Allergen-specific immunotherapy (ASIT) is the only treatment option that can modulate the disease process driving the immune response toward developing tolerance to the offending allergens. The main immunological mechanisms of ASIT include shifting the immune response from Th2 towards a regulatory and/or Th1 response, as well as the induction of IgG antibodies that block the binding of allergen-specific IgE antibodies to the allergens and prevent mast cell degranulation by binding toto the inhibitory FcγRIIb.[162]

Several studies have explored the potential usefulness of ASIT for IBH using whole-body extracts. In a placebo-controlled double-blinded study, 14 privately owned horses completed a six-month trial using an aqueous extract of whole *C. sonorensis* (formerly known as *C. variipennis*).[27] In each group, four owners reported that their horses had improved. No significant statistical difference in efficacy between the two groups was found and improvement was attributed to insect avoidance.

In an uncontrolled study, immunotherapy with *C. sonorensis* (formerly known as *C. variipennis*) combined with 20 µg mycobacterial cell wall fraction (MCWF) as an immunostimulant was conducted in 10 horses for two years.[163] Weekly doses reduced the clinical signs in nine of the 10 horses in the first year. Eight horses were treated with a maintenance dose during a second year. After the second year, three horses were completely free of clinical signs, three showed much less severe clinical signs compared to previous untreated

years, and two showed moderate reduction in clinical signs. Control groups examining the effects of MCWF or the *Culicoides* extract alone were not investigated.

A double-blinded, randomised, placebo-controlled study enrolling 20 IBH horses for a year failed to show any benefit of ASIT using commercially available whole-body extracts.[164] Clinical response was assessed every four months for one year and insect repellent was used weekly in both groups. Differences in clinical scores between groups were nonsignificant at any re-evaluation. The positive improvements noted in both groups are likely to have been a result of to the insecticide treatment.

Although all three studies used crude extracts consisting of hundreds of proteins and possibly lacking a sufficient amount of salivary gland proteins to induce a positive response, combining the crude extract with the adjuvant MCWF may explain the positive response noted in driving the IBH reaction away from Type I and Type IV hypersensitivity reactions towards a Th1 response.

ALLERGEN-SPECIFIC IMMUNOTHERAPY FOR PREVENTION OF IBH

Allergen specific immunotherapy also has been explored to prevent the development of clinical disease in genetically predisposed Icelandic horses. These studies have focused on the ability of ASIT to induce the production of IgG that would block the binding of IgE in IBH horses. None of the published studies has assessed the clinical efficacy of this strategy when these horses are moved to continental Europe.

In a pilot study, 12 horses were vaccinated three times with 10μg of each of the four recombinant *C. nubeculosus* allergens in IC31 adjuvant.[165] Six horses were injected intralymphatically and six were injected intradermally. Antibody responses were measured by immunoblots and ELISA. Testing the blocking activity of the sera from the horses immunised intralymphatically showed that the IgG antibodies generated were able to partly block binding of serum IgE from an IBH-affected horse in vitro. The authors concluded that both intralymphatic and intradermal vaccination of horses with recombinant allergens in IC31 adjuvant induced an immune response without adverse effects and without any IgE production.

In a follow-up study, horses were vaccinated intralymphatically and subcutaneously using *C. nubeculosus* allergens in alum/ Monophosphoryl Lipid A (MPLA) adjuvants.[166] Authors reported that the intralymphatic and subcutaneous administration of small amounts of pure allergens in alum/MPLA induced high IgG antibody levels and Th1/Treg immune responses, and that based on the in vitro response this approach could be a promising strategy for prevention of IBH. No clinical assessment of this approach was done nor in either of the two aforementioned studies were groups treated with just the adjuvants alone to assess their effects on the horses' immune response. A recently published study comparing intralymphatic with subcutaneous injection of r-Culicoides allergens mixed with adjuvants (aluminium-hydroxide-gel and alum/MPLA) for the prevention of IBH found no difference between the routes of administration.[167]

Oral administration of transgenic barley expressing *Culicoides* allergens also was investigated for its ability to induce a specific antibody response.[168] The allergen Cul n 2, a hyaluronidase originating from the salivary gland of *C. nubeculosus*, was expressed in barley. Horses treated with the transgenic barley mounted a Cul n 2-specific IgG response, which was able to partially block serum IgE binding from treated IBH horses in vitro. Another study aimed to compare the used *C. nubeculosus* allergens Cul n 3 and Cul n 4 expressed in transgenic barley grains with the corresponding E. coli or insect cells expressed proteins for measuring antibody responses. The authors evaluated allergen-specific IgG in the sera from 12 horses not exposed to Culicoides, before and after intralymphatic vaccination with *Escherichia coli*-rCul n 3 and 4. Before vaccination no IgG binding to the barley and insect cell produced proteins was detected and a similar increase in specific IgG was observed after vaccination. It was concluded that barley produced allergens are useful for use in immunoassays.[169] None of the mentioned studies evaluated the ability of these strategies to prevent clinical signs upon natural exposure.

Consensus statement on ASIT for IBH

- Evidence is lacking to recommend ASIT as treatment for IBH using the currently available commercial extracts
- Studies are needed to explore benefits of ASIT for the treatment of IBH using recombinant allergens
- The ability to prevent clinical signs of IBH by vaccinating horses with recombinant allergens before natural exposure is unknown. Intradermal, intralymphatic and oral exposure to recombinant allergens leads to an IgG response that appears to partly block binding of *Culicoides*-specific IgE in IBH horses

CYTOKINE VACCINATIONS

IL-5 and IL-31 have been explored as targets for therapy for IBH horses in multiple studies with promising results.[90,94,104] In one clinical trial, horses were injected with virus-conjugated IL-5 three times in the first year and then boosted once in the second year, and demonstrated that the booster in the second year re-induced anti-IL-5 antibodies and produced an improvement of clinical scores.[94] The authors did not specifically measure pruritus and focused on lesional scores. Vaccination was additionally associated with a reduction in blood eosinophil[94] and basophil[170] concentrations.[94]

As yearly boosters were advocated as a long-term strategy to treat IBH horses,[171] it was important to assess the safety of this vaccine in not inducing antibodies directed at cytokines or antigen–antibody complexes. The safety of a Virus-Like Particle-Based Vaccine Targeting Self-Protein IL-5 was investigated

by monitoring B-cell responses, complete cell blood counts and chemistry panels in horses that had enrolled in clinical trials.[172] More specifically, blood samples collected from 34 Icelandic horses enrolled in previously published clinical trials[90,94] were used to monitor IgG responses and cytokine profiles. Horses had received vaccination against IL-5 for a period ranging from two to five years (two years, n = 9; three years, n = 11; four years, n = 4; five years, n = 2). Responses of vaccinated and unvaccinated horses were compared and it was found that no induction of auto-reactive peripheral blood T cells resulted after vaccination and that the T cells of vaccinated horses produced higher levels of gamma IFN-γ. The vaccination induced strong IL-5 antibody titres in all animals and this response was neutralising and not auto-induced. Antibodies produced were mostly of IgG1 and IgG4. There was no induction of immune complex disease and no change in complete cell blood counts and chemistry panel over time in the vaccinated horses. The authors concluded that the vaccine was safe and well-tolerated.

ATOPIC DERMATITIS

Introduction

Atopic dermatitis, defined as an abnormal immunological response to environmental allergens, has come to be accepted as a cause of pruritus and urticaria in horses.[128,129] Atopic dermatitis probably is more common in horses than reported, partially because it can co-exist with IBH, which also can cause pruritus and urticaria.[135,174] Breed predilections have varied depending upon geographical areas, yet Arabians, Finn horses and thoroughbreds have been noted to be commonly affected; there is likely to be a hereditary component.[105,169,173]

Pathogenesis

Robust data are lacking for AD in horses. Our understanding is largely an extrapolation of what we know about AD in other species.[174] The pathogenesis of AD in horses is likely to be mediated (at least initially) by an immune system skewed toward the Th2 response and the production of allergen-specific IgE.[174,175] A significantly greater number of positive reactions on IDT were noted in horses with AD and recurrent urticaria compared to clinically normal horses, providing evidence of a Type I IgE-mediated hypersensitivity for these diseases, although some positive reactions can be seen in normal horses.[176–178]

Most of what is known about the immunopathogenesis of hypersensitivities in horses comes from several elegant studies on IBH showing a dysregulated immune system in which Th2 cytokines, including IL-4, IL-5, IL-6 and IL-13 and IL-31 are upregulated.[68–71,91,92,104] Of these cytokines, IL-31 is a key mediator for itch in humans, dogs, monkeys and mice.[179–182] Its role in equine AD still needs to be fully elucidated although preliminary work shows that IL-31 is a good target to decrease pruritus in IBH horses.[104] IL-31 was reportedly increased in allergen-stimulated peripheral blood mononuclear cells and detectable in skin lesions of IBH-affected horses. Because the development of biological pharmaceutical products is expensive in horses, the approach of this study was to immunise horses to equine IL-31 linked to virus-like particles in order to trigger antibody formation against a self-antigen. Although this approach is reported to be well-tolerated over the course of a few months, care should be used if this strategy is considered for long-term therapy of pruritus.

Another recent study confirmed the role of IL-31 in equine pruritus. In this study the intradermal injection of a recombinant IL-31 induced pruritus in normal horses.[183] Horses showed two different peaks of pruritus after the intradermal injection of the recombinant IL-31. The pruritic effect typically was delayed and possibly linked to the release of other mediators rather than due to the effect of IL-31 per se.

The role of the skin barrier in equine AD has been addressed in very few studies so far. One study showed alterations of lipid lamellae in atopic horses using electron microscopy, namely retained lamellar bodies and amorphous lipid changes similar to reports in other species affected with AD.[184] Other studies have examined trans epidermal water loss (TEWL) in horses demonstrating that breed has an effect on TEWL in healthy horses.[185] This makes assessment of the parameter very complex, and possibly unreliable when applied to a disease state such as AD.

There are currently no published studies on skin barrier repair in atopic horses specifically, although a cream containing omega 3 fatty acids and emollients was useful in *Culicoides*-allergic horses.[155] Some owners of horses with allergic dermatitis believe that a combination of bathing and use of topical essential oils (Dermoscent Essential 6) is helpful (Fadok, unpublished data, 2017–2019). Barrier defects and their potential treatment should be further investigated in horses to determine whether repair is a viable treatment option.

Horses with AD have an altered phospholipid profile in their sera compared to healthy horses, with lower levels of detectable phosphatidylcholine and sphingomyelin.[186] The lipid profile of allergic horses was monitored during therapy and authors found that changes in sphingomyelin correlated significantly with alterations of clinical signs.[187]

Clinical signs

Atopic dermatitis may be a seasonal or, in temperate climates, year-round pruritic dermatitis. Urticaria, urticaria with pruritus, or pruritus alone are the three common presentations of AD. Pruritus most commonly affects the face and trunk.[188,189] Horses manifest pruritus by rubbing against objects (or people), biting or

rolling. Urticaria is usually generalised and not necessarily associated with pruritus. As environmental allergies can co-exist with insect allergy,[189] the distribution of lesions in affected horses can be a combination of environmental and IBH with involvement of the chest, neck, tail and legs.

Summer seasonal signs would be most consistent with allergy to pollens or insect allergy; autumn/winter or year-round signs would be more consistent with an allergy to moulds, barn dust, and/or storage or house dust mites (HDM) or food allergy. Food has been demonstrated to be a trigger for urticaria,[190,191] yet its role in triggering AD flare and pruritus is not clear at this time. It is under investigation as to whether horses may manifest AD in conjunction with respiratory disease, and some researchers have included horses with equine asthma or chronic obstructive pulmonary disease in studies evaluating allergies and/or ASIT.[192,193] Equine asthma has been regarded as being similar to the human counterpart.[194–196]

Atopic dermatitis can start in young adults or later in life especially in horses that have moved from a colder climate to a warmer geographical area. Thus, when clinicians take the history, it is important not just to note the age of the patient at the time of onset of clinical signs and also to consider geographical moves. Over time, a seasonally affected horse may become nonseasonal as the animal has more time to develop sensitivities.

Consensus statement on pathogenesis and clinical signs of equine AD

- A complete understanding on the pathogenesis of equine AD is lacking and most information comes from studies on IBH or AD in other species
- Anecdotal evidence exists about genetic predisposition and co-existence of respiratory and cutaneous manifestations of atopic disease in horses
- The role of allergen-specific IgE has been demonstrated by serological testing, skin testing and positive response to ASIT
- Genetic predisposition is recognised yet not well-studied
- Studies on skin barrier and cytokine dysregulation are needed
- Triggers for AD can include environmental allergens, insects and possibly foods
- Cutaneous signs consistent with AD include seasonal pruritus on the face and flexural surfaces, and sometimes recurrent urticaria
- Co-existence of environmental and insect allergies is common in warm climates and this leads to a combination of clinical signs with IBH

Diagnosis

It is currently accepted that diagnosis of AD is based on clinical signs and the exclusion of other diagnoses (especially IBH and ectoparasite infestation). Allergen-specific IgE testing can be performed to identify allergens to be used for ASIT. Horses with AD and recurrent urticaria generally have a higher incidence of positive reactions than healthy horses, yet the diagnosis cannot solely be made based on the IDT or serological testing.[196] Testing should be interpreted in light of the history and used to determine which allergens might be useful for ASIT.

In one study from Australia, HDM (*Dermatophagoides* spp.) allergens were found on horse rugs and saddle blankets, justifying the inclusion of these allergens in IDT and serological tests.[197] This is supported by a study wherein the most common allergens giving positive responses on IDT were *Culicoides* spp. and the HDM *Dermatophagoides farinae*.[198] Before performing skin testing, recommended minimum withdrawal times are 14 and seven days for oral glucocorticoids and antihistamines, respectively.[199] These recommendations come from the results of a study in which dexamethasone (20 mg) was administered intramuscularly daily for seven days and testing was repeated at 3–4 h, Day (D)7 and D14 after the final dose of dexamethasone.[199] Hydroxyzine (500 mg) was administered orally twice daily at a dose of 500 mg for seven days. Testing was performed 3–4 h, D3 and D7 after the final dose of hydroxyzine. In that study the authors did not find a difference between pre- and post-treatment subjective evaluation of skin test reactivity and the objective measurement of the wheal diameter was smaller after treatment. Wheal diameter returned to pre-treatment levels at D14 after discontinuation of dexamethasone and D7 after discontinuation of hydroxyzine. Withdrawal of drugs is typically not done before serological testing and no study has specifically addressed this issue.

Interestingly, discrepancies in reactivity have been reported when comparing the two sides of the neck in atopic horses in one study.[200] Two studies attempted to determine threshold concentrations of allergens for skin testing – what concentration is less likely to induce an irritant reaction and most likely to induce a clinically relevant reaction.[201,202] Interestingly, both studies cast doubt on the clinical relevance of interpreting skin test reactions at 24 h post-test.

Older studies did not find a good correlation between skin testing and IgE serological testing.[26] However, more recent studies have noted a good correlation, both in atopic horses as well as horses with IBH.[142,203] Possible reasons could be better IgE detection methods, use of clinically relevant threshold concentrations in skin testing and improvement in allergen extracts used. The latter were noted to contain variable amounts of detectable protein in an older study.[204] Poor correlation for most allergens (59 of 61) also was attributed to the high concentrations of allergen-specific IgG in the horse serum, which were found to compete with IgE

for binding to the ELISA plates.[204] The authors of that study concluded that an ELISA using whole serum and crude allergen preparations provides limited diagnostic information in horses.

Horses, like other species, also have IgE against cross-reactive carbohydrate determinants (CCD) and this can lead to positivity on serological testing, which is decreased after inhibition of CCD reactivity.[205]

Consensus statement on diagnosis of equine AD

- Diagnosis is clinical, based on history, clinical signs and exclusion of other pruritic diseases, especially IBH and ectoparasites
- Positive results on allergen-specific IgE tests represent allergens to avoid or to consider for formulation of ASIT based on historical correlation.

Treatment

While in other species, specific guidelines for treatment have been published, no equivalent recommendations exist for horses. Several treatment options have been reported for equine AD, including glucocorticoids, antihistamines, essential fatty acids, pentoxifylline, topical therapy and ASIT.[186,206,207]

Glucocorticoids

Pruritus is a substantial clinical sign in atopic horses, so medical therapy often initially includes the use of glucocorticoids. They are very frequently prescribed by specialists and practitioners alike and should be used judiciously. There are limited controlled studies evaluating the safety and dosing of glucocorticoids for hypersensitivity disorders in horses. Review articles regarding the function, pharmacodynamics, pharmacokinetics, indications for use and adverse effects associated with glucocorticoids are available.[208,209]

Most veterinarians rely on using two systemic glucocorticoids in practice: prednisolone and dexamethasone. Prednisone is not as effective in the horse as prednisolone, owing to poor absorption, rapid excretion and failure of hepatic conversion of prednisone to prednisolone. It is known that after gastrointestinal absorption, prednisone requires conversion to its active metabolite prednisolone in the liver by the action of the 11-B hydroxysteroid dehydrogenase.[210] In one study of horses with chronic obstructive pulmonary disease (COPD), neither prednisone nor prednisolone could be detected after oral administration of prednisone.[211] Consequently, prednisolone is preferred to prednisone in the horse. Depending on the disease severity, dosages may need to be started at the high (1.0 mg/kg) or low end (0.5 mg/kg) of the anti-inflammatory dose range to control the hypersensitivity, and then gradually tapered to the lowest effective dose and frequency, typically every other day or less.[208,212]

In more severe cases, induction dosages of prednisolone can be administered at 1.5–2 mg/kg p.o. once daily for 5–10 days until the clinical signs are controlled, then tapering to the lowest-dose alternate day dose which controls the disease over a period of two to five weeks. Some horses will have limited response to prednisolone and may respond better to either injectable or oral dexamethasone.

Dexamethasone is considered a more potent glucocorticoid; it can be administered intravenously, intramuscularly or orally in the horse.[213] Orally administered dexamethasone showed no significant difference from intravenous administration in terms of endogenous cortisol suppression in healthy horses, nor in relief of clinical signs in horses with recurrent airway obstruction, thus treatment with orally administered dexamethasone for atopic horses may be equally as effective as when given intravenously.[214,215] Dexamethasone formulations vary in their duration of action based on their structure, with short-acting dexamethasone solution products (dexamethasone sodium phosphate) recommended. Often, an initial loading dose of dexamethasone is needed at 0.02–0.1 mg/kg once daily, which may be followed by an oral maintenance dosage of 0.01–0.02 mg/kg every two to three days.[216,217] Dexamethasone can be particularly helpful in more refractory cases.

Triamcinolone acetonide is another potent glucocorticoid and is used infrequently in allergic hypersensitivity disorders in horses owing to concern for potential adverse effects such as steroid hepatopathy and potential development of laminitis.[218–223] When using oral glucocorticoids, writing out the induction, tapering and maintenance dosages on a day-to-day basis as a client handout is extremely helpful. Such a schedule allows safer administration and establishment of a "threshold dose" so that the patient remains disease-free.

The adverse reactions associated with glucocorticoid therapy in horses are numerous and it is beyond the scope of the consensus guidelines to go into details found in other review papers.[218–225] The immune system, musculoskeletal system and gastrointestinal system are some of the more common organ systems that can be affected. Clients also should be warned about the increased risk for infections and the impact on wound healing.

The development of gastric ulcers in horses with chronic glucocorticoid use also has been a topic of concern. However, a previous review of risk factors associated with the development of equine gastric ulcers did not find any correlation between previous corticosteroid administration and gastric ulceration.[226] Nevertheless, caution is recommended when administering glucocorticoids to horses with a previous history of or active gastric ulceration.

One of the most controversial and poorly documented adverse reactions is the development of laminitis in horses treated with glucocorticoids. There are many proposed mechanisms on how glucocorticoids

could cause laminitis. These include vasoconstriction and metabolic effects such as increased circulating insulin or glucose,[234,235] decreased collagen production in the lamellar basement membrane and connective tissue, diminished keratin production in the hoof wall, and diminished growth from the coronary band.[236,237] There are cases of glucocorticoid-induced laminitis reported in the literature yet there is poor scientific evidence actually documenting a direct correlation between the two, with one study showing that laminitis associated with steroid administration occurs only if the horse already has predisposing factors.[231] In two of the larger retrospective reports, the incidence was extremely low (one in 205) looking specifically at triamcinolone[231,232] and three in 2000 cases based on incidence in one veterinary practice following intraarticular administration of primarily triamcinolone.[232] In a comprehensive evidence-based review of 13 publications with 40 cases of corticosteroid-induced laminitis, there was insufficient evidence to support such an association in healthy adult horses. However, there was weak evidence of an association between administration of multiple doses of systemic corticosteroids and the onset of laminitis in adult horses with underlying endocrine disorders or severe systemic disease.[239]

In a retrospective case–control study aimed to investigate whether administration of oral prednisolone increased the risk of laminitis, it was found that of the 416 horses treated with prednisolone, 16 (3.8%) were diagnosed with laminitis.[233] In the 814 horses of the time-matched control group, 46 horses (5.7%) were diagnosed with laminitis. The authors found no significant differences in the overall laminitis incidence rate ($p = 0.8$), incidence rate during prednisolone treatment ($p = 0.09$), or probability of laminitis ($p = 0.3$) between the treated and the control group. In a retrospective study assessing the role of glucocorticoid therapy as a risk factor for the development of laminitis, it was found that the significant associations were breed, weight and the presence of an endocrinopathy, and not steroid use.[234] Practitioners should evaluate every case individually and screen history for pre-existing laminitis or predisposing factors to properly advise owners.

Antihistamines

Antihistamines are reported to provide relief in atopic horses,[217] although the clinical response is variable and very few controlled studies of efficacy have been done in horses. In one retrospective study, most owners of atopic horses reported benefit from antihistamines, and only three of those horses showed drowsiness as an adverse effect.[169] Unfortunately, no details about the type and dosage of antihistamines used was given. Hydroxyzine is considered one of the most frequently used antihistamines for horses.[175,194] It is given at 1–2 mg/kg every 8–12 h. Sedation is the most common adverse effect. The pharmacokinetics of clemastine,[235] fexofenadine[236] and cetirizine[24,238] have been studied in horses. Cetirizine, the active metabolite of hydroxyzine, has a high bioavailability in the horse and is frequently prescribed in clinical practice.

Chlorphenamine has been reported to inhibit wheal formation after intradermal injection of histamine or *Culicoides* antigen in six ponies with IBH, when 12 mg of chlorpheniramine was concurrently injected intradermally.[161] The recommended dose for chlorphenamine is 0.1–0.5 mg/kg twice daily, yet data about bioavailability of chlorpheniramine in horses after oral administration are currently lacking in addition to controlled studies to assess its efficacy to control pruritus in atopic horses. Doxepin is used at a dose of 0.75–1 mg/kg twice daily, and diphenhydramine at 1–2 mg/kg every 8–12 h.[207,208] In summary, antihistamines have been used regularly to treat AD in horses based largely on anecdotal evidence. All antihistamines should be prescribed with care in competing horses, as they are prohibited drugs in competitions in many countries.

Pentoxifylline

Phosphodiesterase (PDE) inhibitors have been evaluated as a group of drugs to help control allergic dermatitis in many species. Pentoxifylline (PTX) is a synthetic xanthine derivative that causes phosphodiesterase inhibition resulting in a variety of dermatological therapeutic and anti-inflammatory effects in both animals and humans.[224–242] It has been empirically used for endotoxaemia, laminitis and airway disease in horses with conflicting results.[242,243]

The exact mechanism of action (MoA) of pentoxifylline in horses has not been determined. Its proposed benefit in vascular diseases is due to its rheological effects of increasing red cell deformability and decreasing platelet aggregation and adhesion, vasoconstriction, plasmin, antithrombin III, fibrinogen, alpha2 antiplasmin, alpha1 antitrypsin and alpha2 macroglobulin.[243–246] It can improve wound healing by increasing fibroblast collagenases, decreasing fibroblast collagen, fibronectin and glycosaminoglycans, and decreasing tumour necrosis factor (TNF) alpha.[247–249] TheMoA of pentoxifylline in allergic skin conditions is due to its ability to inhibit T- and B-cell activation and proliferation, to increase leucocyte deformability and chemotaxis as well as production of IL-10 and prostaglandin (PG)E2, and to decrease leucocyte adhesion and aggregation, neutrophil superoxide release, neutrophil degranulation, monocyte TNF-alpha production, leucocyte response to TNF-alpha, lymphotoxin and interferon-gamma production, leucocyte response to IL-1 and IL-12, and natural killer cell activity.[246–251] No controlled studies exist for its use in equine AD or insect hypersensitivity although anecdotally it is sometimes prescribed.

The current proposed dose is 10–15 mg/kg h. twice daily. However, controversy exists about the pharmacokinetics of the drug in the horse and the exact therapeutically effective dose is not known. Results indicate that PTX is rapidly absorbed and metabolised. Higher

serum PTX concentrations, area under the curve, and bioavailability were observed after the first oral dose (10 mg/kg), compared with the last dose. Both PTX and its metabolite 1-(5-hydroxyhexyl)-3,7-dimethylxanthine (1-M1) reach serum concentrations considered to be therapeutic in humans and therapeutic in horses with endotoxaemia.[252,253]

Drug availability appears to decrease by 30% with multiple dosages and thus the therapeutic efficacy may wane, at which point, one may consider increasing the dose rate to 30 mg/kg/day by either increasing the dosage with twice daily administration or by increasing the dosing frequency to three times daily.[253] In addition to using the drug as a sole therapy, it may have synergistic effects with glucocorticoids and/or have a steroid-sparing effect, and thus may be combined with glucocorticoids and other anti-inflammatory drugs.[254]

Topical therapy

Owing to the large size of horses, topical therapy of generalised pruritus is difficult, cumbersome and sometimes costly. Nevertheless, it is frequently recommended in practice. With localised disease, various topical glucocorticoids have been used as treatment for atopic horses.[207,216,217] Topical corticosteroids have been reported as helpful.[255] However, adverse effects such as localised skin atrophy and alopecia may occur with prolonged use. As with many other treatment options, randomised controlled trials are lacking.

When choosing a topical glucocorticoid, the goal is to select products with minimal adverse effects topically (local cutaneous atrophy, alopecia, comedone formation and secondary infections) and systemically (minimal to no haematological and biochemical changes, suppression of the adrenal axis). A product that is available in many countries outside the USA and which may be a good choice for localised pruritus control in the horse is hydrocortisone aceponate [HCA (Cortavance, Virbac SA or Cortacare, Animalcare Ltd)], available as a 0.0584% spray formulation. As a nonhalogenated, di-ester, topical glucocorticoid, it is associated with better local and systemic tolerance compared to conventional topical glucocorticoids owing to the lack of measurable systemic absorption.[256] Use of this product in cases with localised mane and tail pruritus is ideal with a good short-term response. One study looked at cutaneous atrophy in horses comparing several topical glucocorticoids (hydrocortisone, diflorasone diacetate, mometasone furoate and clobetasol propionate). The thoracic skin was treated daily for 12 days, and the skin thickness was measured by the CT (compression thickness) method. The skin-thinning effects of diflorasone diacetate, mometasone furoate and clobetasol propionate were quite similar. Hydrocortisone showed only a weak skin-thinning effect.[257] The study confirmed that atrophy can occur with some of the more potent glucocorticoids. In addition, the authors feel that the lower limbs of horses are particularly sensitive to this adverse effect and special care needs to be taken when using potent glucocorticoids in that location.

Essential fatty acids

Although many authors recommend the use of essential fatty acids for AD in the horse, studies detailing types of fatty acids, their dosages and efficacies are rare. Essential fatty acid products containing the omega 3 fatty acids eicosapentaenoic acid and docosahexaenoic acid, failed to show significant improvement in one study investigating seasonal pruritus.[258] Most evidence for the use of essential fatty acids in allergic horses has focused on horses with IBH.[155,157]The exact MoA in horses is unclear. There is in vitro evidence for sulfidoleukotriene generation from peripheral blood leucocytes of horses with IBH pointing to a possible role of those molecules in equine allergy.[29] Prostaglandin E2 synthesis was decreased after 14 weeks of fish oil supplementation, a source of omega-3 fatty acids in contrast to corn oil (omega 6) supplementation in healthy horses.[259]

In atopic horses, one randomised controlled study showed a decrease in skin test reactions after 42 days of flax seed supplementation (1 lb/1000 lb body weight/day) compared to controls,[158] supporting the anti-inflammatory action of omega-3 fatty acids in horses. In an open study of 14 horses with IBH, five of 14 showed a very good response and five of 14 showed a good response to being supplemented with 20 g of evening primrose oil (omega 6) and marine fish oil (80:20 mixture) for 13 weeks.[158] In summary, although there is anecdotal evidence for the treatment of equine AD with essential fatty acids, there are few data on the use of fatty acids in equine AD and further trials are needed to identify the best regimen.

Oclacitinib

The pharmacokinetics and the clinical responses to oclacitinib in horses have been preliminarily investigated. In one abstract, a single-dose pharmacokinetic study of oclacitinib in horses following intravenous and oral administration was evaluated. Four horses received 0.25 mg/kg i.v. and six horses received 0.2 mg/kg p.o. In both evaluations, plasma was serially collected for 72 h postdosing and the half-life for both intravenous and oral administration was similar at 9–10 h.[260] This is a longer half-life than that reported in dogs, and therefore plasma concentrations could be maintained with once daily dosing. At a dosage comparable to the approved dosage in dogs, six adult horses were administered a single dose of 0.5 mg/kg oclacitinib maleate. Blood was collected before drug administration and at 15 min, 30 min, 45 min, 1, 2, 4, 6, 8, 12, 24, 48 and 72 h post-treatment. Oclacitinib plasma concentrations were measured by liquid chromatography/mass spectrometry. The estimated $T_{1/2}$ was 7.5–8 h, again confirming a longer half-life than in dogs, and supporting once daily dosing.[261] In another abstract, the efficacy

and safety of two oral doses (0.1 and 0.25 mg/kg once daily) was evaluated over 28 days and compared to a placebo control group. Fifty-eight horses with allergic skin disease were randomised into the treatment groups (placebo, n = 19; 0.1 mg/kg, n = 19; and 0.25 mg/kg, n = 21) Horses were evaluated based on pruritus Visual Analog Scale (PVAS) and clinical lesional scoring. Treatment difference ($p \leq 0.0938$) was found for 0.25 mg/kg dosing compared to placebo beginning at D5 through study evaluation D5, D7, D14, D21 and D28. Lesional scoring was not significant ($p \leq 0.136$). Adverse events and clinical pathological evaluation revealed no effects that appeared clinically significant or biologically important.[262] Further larger controlled clinical studies are needed to fully evaluate the efficacy of oclacitinib compared to glucocorticoids along with long-term safety of oclacitinib in horses with AD. This drug is currently unlicensed in horses.

Allergen specific immunotherapy

Atopic dermatitis has been successfully managed with ASIT, with horses showing improvement as early as two months into treatment.[166] Immunotherapy should be administered at least 12 months before success is evaluated. One study showed an increase in success if horses were evaluated after 24 months of treatment.[176] In horses with a good response, owners typically will discontinue ASIT after six months to eight years (mean 2.2 years).[176] While in other domestic species it is thought that most patients will need to maintained on the immunotherapy for life, in the horse it has been reported that two thirds of patients stayed in remission after cessation of ASIT.[165,197] In general, approximately 70% of atopic horses improve with hyposensitisation.[173] Other researchers have reported both higher (>80%) and lower (56%–64%) results.[187,188,256] Published studies are retrospective and protocols vary in terms of dose, frequency of injections, and use of aqueous or aluminium-precipitated allergens.

Allergen-specific immunotherapy is indicated when offending allergens causing AD cannot be avoided and the disease is severe or affects the horse for an extended time every year. Allergens relevant for each atopic horse are chosen for incorporation into an immunotherapy treatment set based on history, exposure and allergy test results. The clinician also needs to be aware of degree and duration of exposure based on presence of the allergen(s) in the horse's environment. Grass and to a lesser degree weed pollens often are carried many kilometres by the wind, while tree pollens tend to be heavier and thus travel shorter distances. Moulds, and storage mites and HDM also are common in equine environments and may contribute to atopic disease perennially.

Once formulated, the ASIT is then either injected subcutaneously or administered orally in increasing concentrations (induction phase) until a maintenance dose is reached, that is then administered for an extended period of time. Published studies have only reported on the subcutaneous route for ASIT in horses. although sublingual administration has been performed with good results (R.M., unpublished data). Although there are no reported publications on rush immunotherapy (RIT), RIT has been used in horses (R.M., unpublished data). Importantly, the dose and frequency of allergen injections needs to be adapted to the individual horse. Whether the ASIT is based on skin or serological testing for IgE, or both, may not be important in determining the success of the treatment[176]; however, no study in horses has specifically compared the various allergy tests available in identifying allergens for immunotherapy.

In a workshop discussion,[263] in 40 horses with pruritus, urticaria or both, an excellent response to ASIT (e.g. complete remission and no other medications needed) was reported in 20% and a good response in 50% after a minimum of four to six months of therapy. Local swelling at the injection site was mentioned as the most common adverse effect, while one horse developed a systemic reaction characterised by multiple joint effusions.

Horses with positive reactions to environmental allergens (n = 7), insect allergens (n = 6) and both (n = 13) were treated with immunotherapy, and the respective improvements by >50% after 12 months were five of seven, one of six and seven of 13, respectively, and horses with skin disease responded better than those with respiratory signs.[264] Limitations included the retrospective nature, variable and sometimes short duration of therapy, and the definition of improvement as excellent, good or poor based largely on owner evaluation.

In a prospective, double-blinded, placebo-controlled study, 28 horses with positive intradermal reactions to insects and environmental allergens were treated with placebo (n = 14), an extract containing only insect allergens (n = 7) or an extract containing both environmental and insect allergens (n = 7) for three months. The horses treated with allergen extract improved significantly when clinical scores after three and six months were compared to baseline.[265] In the group treated with insect allergens only, one of seven responded completely in the first three months, and clinical scores improved by >50% in 3/7 horses. After six months, the horse that responded completely was still in remission and five of seven had improved by >50%. In the group treated with both environmental and insect allergens, two of seven horses responded by >50% after three months, and after six months, one of seven horses was in remission and two had responded by >50%. This study was prospective, blinded (for the first three months), and lesion scores were defined, yet it was limited by a small number of horses in each group and the short duration of therapy.

In another case series, six related horses with recurrent urticaria were treated with ASIT at a concentration of 20,000 PNU/mL every 21 days. All horses reportedly responded completely to ASIT, with a variable follow-up of two to three years.[173] In a larger retrospective study, 32 owners surveyed after their horse received ASIT at 20,000 PNU/mL, revealed that 27 of 32 (84%) reported a clinical benefit with ASIT based on owner-assessed clinical improvement as well as cessation of

all concurrent therapy in 19 of 32 horses (59%). The mean duration of ASIT in this study was two years with a range of 1–12 years.[173] Fifteen owners (47%) had discontinued ASIT owing to a resolution of clinical signs; a recurrence was seen in five of those horses after one, two (n = 2), three and 12 years, respectively. In three horses, ASIT was restarted, and clinical signs went into remission with treatment.[173]

A recent larger retrospective study also evaluated atopic horses based on an owner survey. In this study, nine of 14 (64%) stated an amelioration of clinical signs with ASIT.[203] Eleven owners discontinued ASIT after the first vial; recurrence of AD was seen in two of those horses and responded again to a re-initiation of ASIT. Localised injection site reactions were occasionally seen in six of 14 patients (43%). Overall, ASIT was well-tolerated in the horses, and severe systemic reaction are extremely rare. The retrospective nature and evaluation of clinical response based on an owner survey are the major limitations of both studies.

The MoA for ASIT in horses has not been completely elucidated. In other species, such as humans and dogs, CD25+ FoxP3+ Treg cells, IL-10 and TGF-beta increase in response to immunotherapy.[266,267] An increase in Tregs downregulates the Th2 response that is crucial for the development of allergic disease. Allergen-specific IgG antibodies also reportedly increase[268] and "block' the binding of allergen-specific IgE antibodies. Evidence in *Culicoides* hypersensitivity suggests that similar mechanisms are involved in horses.[269] Although 56% of horses responded clinically and the percentage of $CD25^{+}$ T cells was higher in horses receiving ASIT, there was no effect of ASIT on the percentage of $CD4^{+}CD25^{high}$ Treg cells, the serum levels of TGF-β, IL-10 and IFN-γ, nor on the serum concentrations of IgA and IgG4 during a one-year treatment period.[270] A reduction in the serum concentrations of total IgE in the horses with allergic dermatitis was observed after six months, and increased again at the end of the study. The authors interpreted these results as indicating that ASIT was insufficient to induce significant changes indicating T-cell tolerance, such as a shift in cytokine production to a more protective Th1 response. An alternative explanation is that the techniques used might not be sufficiently sensitive to detect changes in allergen-specific Treg cells, which is, in fact, the critical feature.

Radwanski et al.[203] demonstrated decreases in allergen-specific IgE and concomitant increases in allergen-specific IgG over the two-year course in their study. They estimated that 76.5% of patients had a positive response to ASIT, based on reduction of pruritus and skin lesions, as well as a reduced need for concomitant medications.

In summary, ASIT has been used successfully for many years in horses with AD resulting from environmental allergies. All published studies are limited by some aspects such as the retrospective or open uncontrolled design, poorly defined treatment outcomes, and small numbers of horses included in the study population. Larger and well-designed studies evaluating immunotherapy in atopic horses are needed. However, all previous studies report similar success rates and the repeated response of horses showing recurrence of clinical signs after cessation of ASIT provides further evidence of the beneficial effects of this treatment option in atopic horses.

Autoserum

Apart from ASIT, another approach to AD (at this point considered experimental) has involved the use of autoserum preparation given orally. The underlying hypothesis is that horses affected by 'summer eczema' (which may include both AD as well as IBH) overproduce lipids that are thereby released into their blood. These lipid particles could form abnormal aggregate complexes that are incapable of interacting with their corresponding receptors on the plasma membrane, thus preventing cell signalling. During the autoserum preparation, these complexes are dissolved, and lipid molecules are again usable for biological reactions.[271] A total of 343 horses were enrolled in a study over a 12-year period and had been allocated to either receive a placebo or autogenous serum.[271] Other treatments were allowed to keep the horses comfortable. Of the 300 horses that received the serum, 70% of them benefited from the treatment based on owners' assessment. Improvement was evident within the first four weeks. The horses that had no improvement were the most severe clinically.

Control of trigger factors

As pruritus is cumulative, it is important for clinicians to identify and control factors that may contribute to the pruritus and flares of AD. The role of infections with *Staphylococcus* spp. in equine AD is unclear, although antibiotics frequently are prescribed and clinical improvement of pruritus is seen when infections are controlled. Whether foods are a trigger in the pathogenesis of AD in horses is unknown[272] (see page 37 for food allergy). Clinicians are encouraged to consider dietary trials to evaluated the role of foods as possible triggers for flares based on the history of each patient as there is no reliable test for food allergies in horses[273]; dietary trials can be considered to address suspected triggers of flares.

The reduction of certain allergens found in higher concentrations inside barns (e.g. dust, moulds) theoretically could benefit AD cases. Such recommendations can be made empirically or based on results of identification of relevant allergens by allergen-specific IgE testing. Dust and moulds can be reduced yet rarely eliminated. Most of the studies regarding dust and mould control have centred around horses with irritant airway disease (IAD), recurrent airway obstruction (RAO) or equine asthma. High concentrations of dust particles and moulds are known to be commonly found in a variety of feeds and bedding materials.[274]

There is good evidence to suggest that reducing airborne dust can improve IAD clinical signs such as coughing and poor performance.[275] Common methods used in horses with respiratory disease include low-dust feed and bedding that produce lower allergen and

particle concentrations compared to hay and straw. One study showed that changing bedding from straw to low-dust cardboard material can cut respirable dust levels in half and reduce mould concentration to negligible levels.[276] Changing feed, especially avoiding hay, has been shown to reduce lung inflammation.[277–279]

Studies have shown that replacing hay feed and straw bedding with a pelleted diet or haylage and wood shavings decreased the respirable dust burden by two- to three-fold and also decreased aeroallergen challenge.[279,280] Immersing hay in water also reduces exposure to respirable dust by approximately 60%.[279] Another study showed that ventilation in stables may help to decrease airborne particles and environmental micro-organisms, as well as reduce tracheal mucus scores, yet the impact on respirable particles and airway cytological findings was questionable.[280]

House dust mites (*D. farinae* and *D. pteronyssinus*) can be found on horse blankets[197] and storage mites (*Tyrophagus, Blomina, Acarus*) that feed on mouldy bedding or hay are impossible to completely eliminate from barn environments. In dust mite-sensitive dogs, the reduction of HDM levels in homes showed moderate-to-good improvement in clinical signs with regular treatment of the environment with benzyl benzoate (Acarosan spray; Allergopharma) along with changing the dogs bedding.[281] Benzyl benzoate also has been used for human dust mite control with more variable results. A Cochrane review showed some promise in the use of environmental acaricides, although the findings from these studies need to be interpreted carefully because of their methodological limitations.[282] No such studies have been performed in barns with allergic horses. Borates killed HDM in carpet and sofas and, when combined with vacuuming, reduced total mites in carpets and mite allergen levels in both carpets and sofas for up to six months.[283] Washing horse blankets in hot water and use of a borate-based miticidal agent (Ecology Works; DustMite Control) in the barn before new bedding is placed in stalls every four to six months may help to minimise dust and storage mite populations. Feeds that are less likely to become mouldy may reduce food sources for storage mites. Simply moving a horse from an indoor barn situation to a pasture also can minimise dust, mite and mould exposure.

Multimodal therapy can be helpful. The additive benefits of combining environmental control with other forms of therapy has been seen in horses with respiratory disease. The positive effects of environment versus environment and anti-inflammatory therapy were evaluated in one study that showed changing to wood shavings and a pelleted diet in place of straw bedding and hay for two weeks resulted in improvement of recurrent airway obstruction (RAO) in 12 horses within three days and continued for seven days.[284] The addition of steroids in this study induced a more rapid reduction in airway inflammation. Overall, airway function was best after 30 days at pasture. The notable improvement in lung function within three days of an environmental modification emphasised the need for allergen reduction.[284]

In conclusion, there is little evidence available in the equine literature on allergic diseases other than those associated with insects. General recommendations can be made for the use of glucocorticoids and ASIT for management, based on published information; however, much work is still needed to satisfy the unmet needs associated with this chronic inflammatory disease in horses.

Consensus statement on treatment for equine AD

- Prospective, controlled studies on treatment options for atopic horses are lacking and are urgently needed.
- In retrospective studies, oral glucocorticoids and antihistamines are commonly prescribed to control clinical signs.
- As AD resulting from environmental triggers can co-exist with IBH, strict insect avoidance is important to optimise response to treatment.
- Management of concurrent bacterial infection is important to address pruritus in atopic patients.
- Environmental control of dust and mould exposure may be beneficial in horses, particularly those with concurrent respiratory disease
- Currently, there is limited evidence to support the use of oclacitinib for the management of equine AD. Once-daily dosing of oclacitinib may have some value in controlling pruritus in horses with AD; however, further controlled studies are needed to further evaluate its safety and efficacy
- Allergen-specific immunotherapy via the subcutaneous route has been reported to be beneficial in horses with AD
- Insufficient information exists regarding the best protocol to use and on immunological changes in the course of ASIT in horses

FOOD-INDUCED DERMATITIS

Understanding food allergy or food-induced dermatitis in horses is considered an unmet need.[273] While the ability of foods to trigger urticaria has been documented in several reports, food as a trigger of AD has not been thoroughly investigated. In the majority of reports, the accepted criteria for diagnosis of food sensitivity – resolution of clinical signs whilst feeding an appropriate elimination diet, return of clinical signs after provocative challenge and subsequent resolution after returning to the strict diet – have not been performed. Food 'allergy' is reported in textbooks[285–287] and described as both a pruritic disease as well as cause for urticarial lesions.[295] Dermatological manifestations linked to foods have been reported in the literature with oats, pasture and pasture plants implicated as possible causes.[287–289] All sources of foods, hays and supplements should be considered when working up cases

of pruritic horses or horses with urticaria. Avoidance of high-protein grasses (e.g. alfalfa, peanut hay) to which horses often react on allergy testing is empirically recommended although no study has been done to back up this recommendation.

Urticaria has been reported anecdotally after ingestion of peanut hay, garlic supplements[290] and concentrated feeds.[169,186] In a more recent report summarising previously published studies,[291] 22 horses with recurrent urticaria were included and intradermally tested with crude extracts of food items and at least one positive reaction was found in 21 of 22 horses. Positive IDT reactions included seven to hays, eight to oats, eight to alfalfa, and commercial supplements. In this report, a restricted diet was given to the 21 horses with a positive food intradermal test, excluding all potentially offending foods for more than a month. Follow-up was possible for 19 horses, with improvement in chronic urticaria noted within three days of the diet change, and no further relapse in 17 of 19 (89%) horses. However, recurrence of clinical signs did not occur upon rechallenge, challenging the notion that the improvement was the result of dietary change.[29]

Dietary restriction is still considered the best method to assess the role of foods as a trigger. Food trials in horses are typically done by selecting a new type of hay that the horse has not eaten in the past and either a simple ingredient-concentrated food containing novel ingredients or avoiding concentrated food if it is not essential to the patient's health. The optimal duration of a food trial in horses is unknown, however improvements have been reported after a few days.[215] Most clinicians recommend a minimum of four weeks for food trials. Age and work requirements should be considered when selecting foods for a trial. Most horse feeds share similar ingredients such as soybean and alfalfa, and thus switching from one brand to another of commercial horse feed is not equivalent to a suitable food trial. Vacuum-packed hay with added vitamins and minerals and no flavouring can be an option to supplement horses that do have high caloric requirements.

Serological testing for foods has been reported to be unreliable. In one study healthy ponies and horses suspected of food allergy were serologically tested to detect food-specific IgE.[273] Consistency of serological test results was evaluated at different time points and in ponies after challenges with suspected allergens. Only seven of 17 ponies were negative on the IgE-based test at the two time points, three had positive results twice and only one tested positive twice for the same food allergen. No abnormalities were noted during the provocation trials. Positive results in normal horses are inconsistent and do not correlate with response to clinical challenge.

Sensitivity to a variety of hays can be found easily on intradermal skin testing of atopic horses yet it is unclear how much of that is an actual food 'allergy' and how much is simple sensitisation resulting from epicutaneous exposure. Grasses are commonly included in immunotherapy for those horses. Whether grass allergies are linked to a food-induced dermatitis or epicutaneously triggered dermatitis is unknown at this time.

Consensus statement

- Currently food allergy in horses is not well-understood.
- Foods have been described as triggers of urticaria and pruritus in horses yet well-defined cases fulfilling the accepted criteria for diagnosis by elimination diet and provocative dietary challenge are not reported.
- A food trial selecting a novel source of hay with appropriate vitamin and mineral supplementation is the only reliable tool at this time to diagnose a food-related disease.
- Serological test cannot be recommended at this time to diagnose a food allergy in horses

CHRONIC URTICARIA IN HORSES

Chronic urticaria is a common and frustrating presentation in equine practice that is not linked to one specific trigger.[293,294] Development of urticaria may or may not be linked to an immunological response.[295,296] Immunologically-mediated urticaria has been traditionally viewed as a Type I hypersensitivity to an allergen with subsequent mast cell degranulation, and release of histamine and other pro-inflammatory mediators.[297] Identifying and avoiding the offending allergen is thus crucial to the long-term management of urticaria. Allergens described to be possible triggers for urticaria range from insects to environmental allergens, foods, oral supplements, drugs and vaccines.[168,216,217] Type II and Type III hypersensitivities also have been described as mechanisms of urticaria.[298] In people, the binding of IgG auto-antibodies to IgE or the receptors for IgE on mast cells make up 50% of chronic urticaria patients.[298] In these patients, urticaria is not triggered by an allergen and can be extremely frustrating to manage. It is highly possible that some of the chronic idiopathic cases of urticaria in horses may fall into this category.

Mast cell degranulation also can occur in ways that are not linked to a hypersensitivity.[299] It can be triggered by exercise,[300] physical stimuli such as pressure (dermatographism),[301] thermal stimuli[302] and psychogenic stresses.[303,304] In equine medicine there are very few documented reports of these types of urticaria. Cholinergic pruritus, considered a variant of cholinergic urticaria, has been described in a horse[305] and sweat-induced urticaria has been reported.[306] The role of IgE has been documented in a study that analysed IgE-bearing cells in horses with urticaria.[307] Horses with urticaria had significantly more IgE-bearing cells in the subepidermal dermis than control horses.

Biopsies of lesional and nonlesional skin of horses with recurrent urticaria also have been studied for their inflammatory infiltrate.[308] Immunohistochemical

evaluation was used to identify various cell populations. Eosinophils were significantly increased in lesional skin together with CD79$^+$ B cells, MAC387$^+$ macrophages and tryptase-positive mast cells. Expression of IL-4, IL-13, TSLP and IL-4 receptor-α was reported to be increased in lesional skin of horses affected by recurrent urticaria compared with control horses. The authors concluded that Th2 cells, eosinophils, mast cells and presumed macrophages play a role in this disease.

Urticarial horses clinically present with hives or wheals.[309] Lesions are common on the neck, sides and face, and may be present anywhere on the body. These lesions are soft and blanch under digital pressure as they are initially caused by vasodilation. Over the course of hours, lesions become firmer owing to the accumulation of inflammatory cells. Individual lesions may wax and wane and, in severe cases, can coalesce into large areas of raised plaques. Horses may or not be pruritic. As lesions develop, the oedema accumulates ventrally and exudation of fluid through the skin can be easily seen on the ventral neck and ventral abdomen. In most cases the onset of the lesions is acute. It is important to enquire what exposure occurred in the hour(s) before development of the lesions to establish a possible link between the onset of urticaria and a trigger. Chronic cases have waves of hives over the course of weeks often without an identifiable trigger.

The diagnosis of urticaria is a clinical diagnosis and in most cases, biopsies of lesions are not taken. A disease that can resemble urticaria in horses is erythema multiforme, a rare immune-mediated skin disease triggered by antigenic stimulations like drugs and vaccines. For cases in which the lesions are firmer and do not indent with digital pressure, a biopsy may be needed to discriminate between the two differentials. Sometimes owners may mistake superficial pyoderma for urticaria as a consequence of the raised hair caused by follicular inflammation more obvious in animals with short hair coats.

Allergen-specific IgE testing may help in the identification of potential offending allergens although having a positive allergy test does not necessarily indicate causation and those results need to considered in conjunction with the horse's history of exposure. Horses with chronic urticaria also were reported to have more positive reactions on intradermal skin test than normal horses.[176,310]

Common treatments for equine urticaria include glucocorticoids such as prednisolone and dexamethasone and a variety of antihistamines.[292,294,307,311] Common choices of antihistamines are hydroxyzine, chlorpheniramine, cetirizine and diphenhydramine.[293–296] Of interest, a recently published study reported on the poor oral bioavailability of oral diphenhydramine in horse highlighting the need for injectable administration.[312] Pentoxifylline and essential fatty acids may be tried for chronic cases.[296]

Currently, there is no published controlled study to evaluate the efficacy of one choice over the other as far as treatment options. Most of the publications are case reports, retrospective case series and reviews.[169,188,285,287,294] Thus, the choice of treatment typically is based on the clinician's preference, acute clinical presentation versus chronic course, and patient's specific needs.

Consensus statement on recurrent urticaria

- Our understanding of equine recurrent urticaria remains limited
- Equine urticaria can be multifactorial and has been reported to be IgE-mediated with mast cell degranulation and Th2-skewed immune response
- Studies on the various factors involved in mast cell degranulation are needed to improve the long-term management of affected horses
- Accurate history is crucial to identify possible triggers.
- Food trials should be considered in animals with chronic recurrent disease
- Various treatments have been used yet no controlled studies could be found in the literature

Final take home points on equine allergies

- IBH is a severely pruritic disease that has a significant impact on quality-of-life of affected horses and their owners
- Much of our knowledge on equine allergic skin disease relates to IBH
- The role of IgE has been documented for IBH, AD and urticaria
- The role of skin barrier in equine allergies is largely unknown
- Very little is known about the pathogenesis of equine AD
- The role of foods as triggers for equine pruritus and AD is unknown
- In general, there is very little evidence-based information on the treatment of equine allergic skin diseases
- General recommendations can be made for the use of glucocorticoids and allergen specific immunotherapy in equine AD, based on retrospective published information; however, much work is still needed to satisfy the unmet needs associated with this chronic inflammatory disease in horses.
- Prospective, controlled studies on therapeutic options for atopic and IBH horses are needed
- Currently, the most documented effective treatment for IBH is insect avoidance together with symptomatic therapy as needed
- Cytokine vaccinations appear to provide relief of clinical signs in IBH and horses with pruritus associated with other allergies
- Retrospective uncontrolled evidence exists on the beneficial effect of ASIT for AD

AUTHOR CONTRIBUTIONS

R. Ma.: Conceptualisation; investigation; writing – original draft; writing – review & editing; validation; methodology. **S. W.:** Investigation; writing – review & editing; writing – original draft. **V.A. F.:** Conceptualisation; investigation; writing – original draft; writing – review & editing; methodology. **D. W.:** Conceptualisation; investigation; writing – review & editing; writing – original draft. **R. Mu.:** Conceptualisation; investigation; writing – original draft; methodology; writing – review & editing. **C. O.:** Investigation; writing – original draft; writing – review & editing. **W. R.:** Conceptualisation; investigation; writing – original draft; writing – review & editing.

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Résumé

Contexte: Les dermatoses allergiques sont courantes chez les chevaux dans le monde entier. Les causes les plus fréquentes sont les piqûres d'insectes et les allergènes environnementaux.

Objectifs: Examiner la littérature actuelle et établir un consensus sur la pathogénie, le diagnostic, le traitement et la prévention.

Matériels et méthodes: Les auteurs ont passé en revue la littérature jusqu'en novembre 2022. Les résultats ont été présentés au « North America Veterinary Dermatology Forum » (2021) et à l'« European Veterinary Dermatology Congress » (2021). Le rapport a été soumis organisations membres de l'Association mondiale de dermatologie vétérinaire afin de recueillir leurs commentaires.

Conclusions et pertinence clinique: L'hypersensibilité aux piqûres d'insectes (IBH) est l'affection cutanée allergique la mieux caractérisée. Une réponse médiée par les immunoglobulines (Ig)E contre les antigènes salivaires des Culicoides est largement documentée. Des facteurs génétique et les environnementaux jouent un rôle important. Des tests suffisamment sensible et spécifique font défaut, et le diagnostic de l'IBH est fondé sur les signes cliniques, la saisonnalité et la réponse au contrôle des insectes. Les éosinophiles, l'interleukine (IL)-5 et l'IL-31 sont explorés comme cibles thérapeutiques. Actuellement, le traitement le plus efficace consiste en l'éviction

parasitaire. Les données actuelles ne permettent pas de recommander l'immunothérapie spécifique (ASIT) avec des extraits de culicoïdes disponibles dans le commerce. L'hypersensibilité aux allergènes environnementaux (dermatite atopique) est le second type d'allergie le plus fréquent. Une implication des IgE est étayée par les tests sérologiques et cutanés et la réponse favorable à l'ASIT. Les études prospectives, contrôlées et randomisées sont limitées et le traitement repose en grande partie sur les glucocorticoïdes, les antihistaminiques et l'ASIT selon les données des études rétrospectives. Les aliments sont des déclencheurs connus de l'urticaire, mais leur rôle dans les dermatites prurigineuses est inconnu. L'urticaire récurrente est courante chez les chevaux, mais notre compréhension est limitée et axée sur la réponse des cellules IgE et T-helper 2. Des études prospectives contrôlées sur les traitements de l'urticaire font défaut. Les glucocorticoïdes et les antihistaminiques sont les principaux traitements rapportés.

Resumen

Introducción: Las enfermedades alérgicas de la piel son comunes en los caballos en todo el mundo. Las causas más comunes son las picaduras de insectos y los alérgenos ambientales.

Objetivos: Revisar la literatura actual y brindar consenso sobre patogenia, diagnóstico, tratamiento y prevención.

Materiales y Métodos: los autores revisaron la literatura hasta noviembre de 2022. Los resultados se presentaron en el Foro de Dermatología Veterinaria de América del Norte (2021) y el Congreso Europeo de Dermatología Veterinaria (2021). El informe estuvo disponible para las organizaciones miembros de la Asociación Mundial de Dermatología Veterinaria para recibir comentarios.

Conclusiones y relevancia clínica: clínica- La hipersensibilidad a las picaduras de insectos (IBH) es la enfermedad alérgica de la piel mejor caracterizada. Una respuesta de inmunoglobulina (Ig)E contra antígenos salivales de Culicoides está ampliamente documentada. La genética y los factores ambientales juegan un papel importante. Faltan pruebas con alta sensibilidad y especificidad, y el diagnóstico de IBH se basa en los signos clínicos, la estacionalidad y la respuesta al control de insectos. Los eosinófilos, la interleucina (IL)-5 y la IL-31 se exploran como dianas terapéuticas. Actualmente, el tratamiento más efectivo es evitar los insectos. La evidencia existente no respalda la inmunoterapia específica de alérgenos (ASIT) con extractos de Culicoides disponibles comercialmente. La hipersensibilidad a los alérgenos ambientales (dermatitis atópica) es la siguiente alergia más común. El papel de la IgE está respaldado por la investigación serológica, los estudios de pruebas cutáneas y la respuesta positiva a ASIT. Los estudios prospectivos, controlados y al azarson limitados y el tratamiento se basa en gran medida en glucocorticoides, antihistamínicos y ASIT según estudios retrospectivos. Los alimentos son desencadenantes conocidos de la urticaria, pero se desconoce su papel en la dermatitis pruriginosa. La urticaria recurrente es común en los caballos, sin embargo, nuestra comprensión es limitada y se centra en la respuesta de las células IgE y T-helper 2. Faltan estudios prospectivos y controlados sobre tratamientos para la urticaria. Los glucocorticoides y los antihistamínicos son los principales tratamientos reportados. Actualmente, el tratamiento más efectivo es evitar los insectos. La evidencia existente no respalda la inmunoterapia específica de alérgenos (ASIT) con extractos de Culicoides disponibles comercialmente. La hipersensibilidad a los alérgenos ambientales (dermatitis atópica) es la siguiente alergia más común. El papel de la IgE está respaldado por la investigación serológica, los estudios de pruebas cutáneas y la respuesta positiva a ASIT. Los estudios prospectivos, controlados y al azar son limitados y el tratamiento se basa en gran medida en glucocorticoides, antihistamínicos y ASIT según estudios retrospectivos. Los alimentos son desencadenantes conocidos de la urticaria, pero se desconoce su papel en la dermatitis pruriginosa. La urticaria recurrente es común en los caballos, sin embargo, nuestra comprensión es limitada y se centra en la respuesta de las células IgE y T-helper 2. Faltan estudios prospectivos y controlados sobre tratamientos para la urticaria. Los glucocorticoides y los antihistamínicos son los principales tratamientos reportados.

Zusammenfassung

Hintergrund: Allergische Hauterkrankungen kommen bei Pferden auf der ganzen Welt häufig vor. Die häufigsten Ursachen sind Insektenstiche und Umweltallergene.

Ziele: Das Ziel dieser Studie war die Durchführung einer Review der momentanen Literatur und Darstellung eines Konsenses in Bezug auf die Pathogenese, die Diagnose, die Therapie und die Vorbeugung.

Materialien und Methoden: Die Autoren überprüften die Literatur bis in den November 2022. Die Ergebnisse wurden beim North American Veterinary Dermatology Forum (2021) und beim Europäischen Veterinärdermatologie Kongress (2021) präsentiert. Der Bericht wurde Mitgliedsorganisationen der World Association for Veterinary Dermatology für ein Feedback zur Verfügung gestellt.

Schlussfolgerungen und klinische Bedeutung: Die Insektenstich Hypersensibilität (IBH) ist die am besten beschriebene allergische Hauterkrankung. Eine Immunglobulin (Ig) E Antwort auf *Culicoides* Speichelallergene ist häufig beschrieben. Die Genetik und Umweltfaktoren spielen dabei eine wichtige Rolle. Es fehlen Tests mit hoher Sensibilität und Spezifität und die Diagnose von IBH basiert auf klinischen Zeichen, Saisonalität und Reaktion auf Insektenkontrolle. Eosinophile, Interleukin (IL)-5 und IL-31 werden als therapeutische Angriffspunkte untersucht. Zurzeit ist die Insektenvermeidung die am besten wirksame Therapie. Die bestehende Evidenz spricht nicht für eine Allergen-spezifische Immuntherapie (ASIT) mit kommerziell verfügbaren *Culicoides* Extrakten. Die Hypersensibilität auf Umweltallergene (Atopische Dermatitis) ist die zweithäufigste Allergie. Eine Rolle für IgE wird durch serologische Untersuchungen, Hautteststudien und positive Reaktionen auf ASIT gestärkt. Prospektive,

kontrollierte, randomisierte Studien sind limitiert und die Behandlung stützt sich hauptsächlich auf Glukokortikoide, Antihistamine und ASIT basierend auf retrospektiven Studien. Futter stellen bekannte Auslöser für Urticaria dar, allerdings ist ihre Rolle bei der juckenden Dermatitis unbekannt. Wiederkehrende Urticaria treten bei Pferden häufig auf, unser Verständnis ist diesbezüglich aber limitiert und konzentriert sich auf Reaktionen von IgE und T2-Helferzellen. Prospektive kontrollierte Studien über die Behandlungen von Urticaria fehlen. Glukokortikoide und Antihistamine sind die am häufigsten beschriebenen Behandlungen.

要約
背景: アレルギー性皮膚疾患は世界中の馬でよく見られる。主な原因は虫刺されや環境アレルゲンである。
目的: 本研究の目的は、 現在の文献をレビューし、病態、診断、治療、予防に関するコンセンサスを得ることであった。
材料と方法: 著者らは 2022 年 11 月までの文献をレビューした。結果は、North America Veterinary Dermatology Forum(2021年)およびEuropean Veterinary Dermatology Congress(2021年)で発表した。報告書は世界獣医皮膚科学会の会員団体に提供し、フィードバックを得た。
結論と臨床的関連性: 虫刺され過敏症(IBH)は、最も特徴的なアレルギー性皮膚疾患である。サシバ工の唾液抗原に対する免疫グロブリン(Ig)E応答は広く報告されている。遺伝および環境因子が重要な役割を果たす。IBHの診断は、臨床症状、季節性、防虫への反応に基づいて行われる。好酸球、インター口イキン(IL)-5、IL-31が治療標的として探索されている。現在のところ、最も効果的な治療法は昆虫の忌避である。既存のエビデンスは、市販のサシバ工抽出物を用いたアレルゲン特異的免疫療法(ASIT)を支持しない。環境アレルゲンに対する過敏症(アトピー性皮膚炎)は、次に多いアレルギーである。IgEの役割は、血清学的調査、皮膚試験、およびASITに対する陽性反応によって裏付けられている。プロスペクティブな無作為化対照試験は限られており、治療は主にグルココルチコイド、抗ヒスタミン剤、レトロスペクティブな研究に基づくASITに頼っている。食品は蕁麻疹の誘因として知られているが、痒みのある皮膚炎におけるその役割は不明である。蕁麻疹の再発は馬によく見られるが、我々の理解は限られており、IgEとヘルパーT2細胞反応に焦点を当てている。蕁麻疹の治療法に関するプロスペクティブな対照試験は不足している。グルココルチコイドと抗ヒスタミン剤が主な治療法として報告されている.

摘要
背景: 过敏性皮肤病在世界各地的马中很常见。最常见的原因是昆虫叮咬和环境过敏原。
目的: 回顾现有达成共识的文献 , 就发病机制、诊断、治疗和预防。
材料和方法: 作者回顾了截至2022年11月的文献。研究结果在北美兽医皮肤病论坛(2021)和欧洲兽医皮肤病大会(2021)上公布。该报告可供世界兽医皮肤病学协会的成员组织反馈。
结论和临床相关性: 虫咬超敏反应(IBH)是最具特征的过敏性皮肤病。针对库蚊唾液抗原的免疫球蛋白(Ig)E反应已被广泛记录。遗传和环境因素起着重要作用。缺乏高灵敏度和特异性的测试 , IBH的诊断是基于临床症状、季节性和对昆虫控制的反应。嗜酸性粒细胞、白细胞介素(IL)-5和IL-31被探索作为治疗靶点。目前 , 最有效的治疗方法是避开昆虫。现有证据不支持使用市售库蚊提取物的过敏原特异性免疫疗法(ASIT)。对环境过敏原过敏(特应性皮炎)是第二常见的过敏。血清学调查、皮肤试验研究和ASIT阳性反应支持了IgE的作用。前瞻性、对照、随机研究有限 , 治疗主要依赖于基于回顾性研究的糖皮质激素、抗组胺药和ASIT。食物是已知的荨麻疹诱因 , 但它们在瘙痒性皮炎中的作用尚不清楚。复发性荨麻疹在马中很常见 , 但我们的理解有限 , 主要集中在IgE和辅助T细胞2的反应上。缺乏关于荨麻疹治疗的前瞻性对照研究。糖皮质激素和抗组胺药是主要的治疗方法.

Resumo
Contexto: Dermatopatias alérgicas são comuns em equinos em todo o mundo. As principais causas são picadas de insetos e alérgenos ambientais.
Objetivos: Revisar a literatura atual e produzir um consenso sobre patogênese, diagnóstico, tratamento e prevenção.
Materiais e métodos: Os autores revisaram a literatura até novembro de 2022. Os resultados foram apresentados no *North America Veterinary Dermatology Forum* (2021) e *no European Veterinary Dermatology Congress* (2021). O relatório estava disponível para as organizações membro da *World Association for Veterinary Dermatology* para que dessem seu *feedback*.
Conclusões e Relevância Clínica: Hipersensibilidade a picada de insentos (IBH) é a dermatopatia alérgica melhor caracterizada. Resposta mediada por imunoglobulina (Ig)E contra antígenos salivares de *Culicoides* é amplamente documentada. Genética e fatores ambientais possuem participação importante. São poucos os testes com alta sensibilidade e especificidade, e o diagnóstico de IBH é baseado em sinais clínicos, sazonalidade e resposta ao controle de insetos. Eosinófilos, interleucina (IL)-5 e IL-31 estão sendo exploradas como alvos terapêuticos. Atualmente, o tratamento mais eficaz é evitar o contato com os insetos. As evidências existentes não corroboram com a utilização de imunoterapia alérgeno-específica (ASIT) utilizando extratos comerciais de *Culicoides*. Hipersensibilidade a alérgenos ambientais (dermatite atópica) é a segunda alergopatia mais comum. Investigação sorológica, testes cutâneos e resposta positiva à ASIT confirmam a participação de IgE. Estudos prospectivos placebo-controle randomisados são limitados e o tratamento é feito com glicocorticoides, antihistamínicos e ASIT baseado em estudos retrospectivos. Alimentos são gatilhos conhecidos para urticária, mas a sua participação em dermatopatias pruriginosas é desconhecida. Urticária recorrente é comum em equinos, apesar de o nosso conhecimento ser ainda limitado e focado em IgE e respostas de células T-helper 2. Faltam estudos prospectivos e controlados sobre tratamentos para urticária. Glicocorticoides e antihistamínicos são os principais tratamentos relatados.