

Comparison of three clinical scoring systems for *Culicoides* hypersensitivity in a herd of Icelandic horses

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Background – *Culicoides* hypersensitivity (CH), an intensely pruritic and seasonal allergic dermatitis, is a common allergic disease affecting horses worldwide. Currently, there is no validated clinical scoring system for the quantification of clinical signs associated with CH.

Objectives – To (i) determine the best cut-off point of three scoring systems, (ii) test the accuracy of each system when compared to the clinical diagnosis of an experienced veterinarian and (iii) assess agreement between systems.

Animals – Icelandic horses (n = 20); eight with CH and 12 unaffected, from a research herd receiving no treatments for allergic dermatitis.

Methods and materials – Lesion scores were recorded biweekly from April until September with three clinical scoring systems (A, B and C) by a single observer initially blinded to CH status. Separate logistic regression analyses for each time point were used to determine appropriate cut-offs for CH classification. Spearman's rho and Cohen's kappa were calculated to analyze correlation of scores and agreement of CH categorization between systems, respectively.

Results – The best allergic cut-off scores for system A, B and C were determined to be three, eight and 12, respectively. For each system median areas under the curve (>0.85) were excellent and discriminatory ability for correctly classifying CH status was strong. Excellent correlation between scores for each system (Spearman's rho > 0.96) and excellent intersystem agreement for CH categorization (kappa ≥ 0.73) were found across scoring time points.

Conclusion and clinical importance – Results support the use of these scoring systems as templates for the future standardization of a CH clinical scoring system.

Introduction

The most common cause of allergic dermatitis in horses worldwide is the seasonally recurrent, intensely pruritic, immunoglobulin E (IgE)-mediated hypersensitivity reaction to salivary proteins (allergens) of the *Culicoides* midge.^{1–6} This disease has been referred to as *Culicoides* hypersensitivity (CH), insect bite hypersensitivity (IBH), sweet itch, summer eczema or Queensland itch in the veterinary literature. A large volume of research exists confirming *Culicoides* species as the causal agent of this allergic disease, including the production of *Culicoides*-

specific IgE antibodies against *Culicoides* salivary gland allergens.^{7,8} Clinical signs of CH are not observed in Icelandic horses while living in their native Iceland, which is free of *Culicoides* spp, whereas signs frequently occur after export.^{6,7,9–12} Native Icelandic horses that have been exported also have a higher prevalence of CH (34.5–60%) than Icelandic horses born in a country where *Culicoides* species are indigenous.^{1,10–16} Therefore, this allergic disease can be precisely referred to as CH.³

The diagnosis of CH is still based largely on expert assessment utilizing the presence of the representative lesions in combination with the history of seasonal pruritus in the summer months and improvement of clinical signs in response to environmental management.^{1,17} However, due to the lack of a standardized clinical scoring system, quantification of disease severity and response to therapeutic intervention varies between research studies, hampering the ability to compare study outcomes between existing publications. Protocols for determining CH status vary significantly and range from owner-completed questionnaires to demonstration of representative clinical signs.^{10,11,18,19}

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Advances in allergen discovery for CH provide a baseline for both improved diagnostic methods with specific allergen(s) and new promising tools for targeted allergen immunotherapy (AIT) using the major allergens of *Culicoides*,^{1,17,20,21} and active vaccination against interleukin-5 (IL-5).²² Therefore, an accepted clinical scoring system to quantify the severity of CH would allow for a more uniform evaluation of clinical response to therapeutic or preventative approaches. Clinical scoring systems have been used in research studies to describe CH status and provide a quantitative result for treatment interventions; however, formal publications of these scoring systems are limited.^{17–19,22,23} Currently, there is no accepted and validated scoring system for CH that objectively quantifies in a single assessment the severity of the clinical lesions associated with CH. To the best knowledge of the authors, multiple systems are being used without accepted cut-off values or formal validation.

The objectives of this study were to evaluate and compare three clinical scoring systems that are currently used in research settings to aid in quantification of CH lesions as well as to monitor response to therapeutic interventions. We hypothesized that each scoring system evaluated would have high discriminatory ability to correctly classify the CH status of both affected and unaffected horses, and that all systems would agree well with one another.

Methods and materials

Horses and *Culicoides* exposure

Twenty Icelandic horses (15 mares, four geldings and one stallion) residing in a research herd were enrolled in the study in April 2017 before the *Culicoides* season and when there were no clinical signs of CH present. Horses had either been imported from Iceland and transported directly to the herd housing facility in Ithaca, NY, USA, or had been foaled at this facility.²⁴ Thus, all horses had lived in an environment with the same local *Culicoides* exposure since they had arrived in the USA or from the time of their birth. Horses were housed in herds on large pastures year-round with free access to run-in sheds and water. Grass hay was fed to the horses *ad libitum* in April and May. *Culicoides* midges were present in the environment

and horses were naturally exposed to these insects from mid-May to mid-October. No CH treatments, including fly preventatives or systemic or topical antimicrobial therapy, were used on the horses throughout the observation period. All horses were vaccinated against rabies virus, tetanus, West Nile virus, Eastern and Western encephalitis virus annually, and were dewormed on a regular basis. The animal procedures were covered under a protocol approved by the Institutional Animal Care and Use Committee of Cornell University (protocol #2017-0005). Upon completion of the study, all horses continued to reside at the research facility.

Determination of CH history

The CH status of each horse was determined before the beginning of the study by an independent investigator based on each animal's medical history before 2017 (Table 1). In addition, serological and cellular immune responses to *Culicoides* had been monitored monthly since the horses came to the United States (2012, 2013 or 2016) or were foaled at the research facility (2012 or 2013). Eight Icelandic horses (6–14-year-old; seven mares and one gelding) were considered to have CH based on seasonally recurrent and pruritic skin lesions which regressed in the winter months. These lesions included crusted papules, excoriations, lichenification, and/or alopecia on the face, chest and/or ventrum, and mane and/or tail rubbing. *Culicoides* as the cause of clinical allergy in the allergic group was supported by intradermal test results obtained in years before this study and all allergic horses had been imported from Iceland. Twelve healthy (control) Icelandic horses (4–11-year-old; eight mares, three geldings and one stallion) had no history of clinical signs consistent with CH. Control horses had either been imported from Iceland or foaled at the facility.

Clinical scoring systems

Clinical scoring systems A, B and C are represented in Figures S1, S2 and S3; the scoring for systems A and B was performed as detailed in the Figures. Severity of lesions was based on clinical judgement by the observer where there were no explicit instructions provided. Scoring for system C was performed as described previously with the following modification: data points were organized in a different arrangement.²² All points were summed to produce a total lesion score for each time point. The ranges of possible lesion scores for each system were as follows: A = 0–10; B = 0–504; C = 0–308.

Assessment of clinical scores

All horses were scored every two weeks from April to September with the exception of a one-week interval between the first two scoring time points. For scoring and recording of data, horses were

Table 1. Age, date of import and *Culicoides* hypersensitivity (CH) history of Icelandic horses (n = 20) in this study

Horse ID	Date of birth	Gender	Origin	Date imported to USA	First year of CH	CH (Y/N)
1	2005	Mare	Iceland	February 2012	2013	Y
2	2007	Mare			2013	Y
3	2006	Mare				N
4	2004	Mare			2013	Y
5	2004	Mare			2013	Y
6	2003	Mare			2013	Y
7	2005	Mare		July 2016	2016	Y
8	2009	Mare				N
9	2009	Mare			2016	Y
10	2012	Mare				N
11	2012	Stallion				N
12	2011	Mare		April 2013		N
13	2011	Gelding				N
14	2011	Mare				N
15	2011	Gelding			2015	Y
16	2011	Gelding				N
17	2012	Gelding	USA	NA		N
18	2012	Mare				N
19	2012	Mare				N
20	2013	Mare				N

brought into a barn with individual box stalls. Scoring began at 07:00 h each time. A single trained veterinary researcher who had no previous experience with the scoring systems and who remained blinded to the determined CH status until completion of data collection performed the clinical scoring.

Statistical analysis

For each time point, data were summed to provide a total lesion score for each horse and system. Total lesion scores from the three scoring systems were compared for each individual time point by logistic regression analysis. Initial data points obtained in April (before the horses showed clinical signs of CH) were excluded from statistical calculations due to the absence of lesions. Time periods were assessed individually to address the repeated nature of the data and fulfil model assumptions. Logistic regression analysis was performed using commercially available software (JMP v11.0, SAS Institute; Cary, NY, USA) to determine the receiver operator characteristic area under the curve (ROC AUC). Based on ROC curves, the cut-off point that maximized correct classification of CH status was determined for each system and time point. Correlation of scores between systems for each time point was analyzed using Spearman's rho. Agreement of CH classification between the three systems was calculated using Cohen's kappa. All data are presented as medians with ranges unless otherwise noted.

Results

Clinical evaluation

Only minor clinical lesions were present during the first four time points of evaluation (mid-April to the beginning of May). In early May, the first *Culicoides* activity was observed and the onset of clinical lesions began in late May. As the summer progressed, clinical lesions and total scores increased and peaked in July and August (Figure 1). A slight decline in lesions was noted in the beginning of September. Clinical scores of nonallergic control horses remained low during the entire evaluation period with occasional mild mane and tail lesions during the summer months (Figure 1). Time spent scoring a horse with each system decreased as the observer became more familiar with the systems; System A took three to five minutes, System B 10–15 min and System C 15–20 min.

No dorsal lesions, other than mane and tail lesions, were present in any of the observed allergic horses. To describe the distribution of lesions recorded in this study, one time point at which clinical signs reached greatest severity (July 25) was examined. At this time point the distribution of lesions in the eight allergic horses were as follows: ventrum in seven horses (87.5%); tail, face and chest in each of six horses (75%); mane in five horses (62.5%); distal limb in four horses 50%; and shoulder in two horses (25%). Figure 2 illustrates clinical lesions representative of the most commonly affected locations with lesions approaching maximum severity. After July 25, clinical lesions changed in intensity and chronicity but no new body sites were affected.

Allergic cut-offs and discriminatory ability of the three scoring systems

The ROC-AUC analysis was performed for each time point to objectively determine the best preliminary allergic cut-off for each scoring system. These cut-offs were defined as the numeric scores at which the most horses

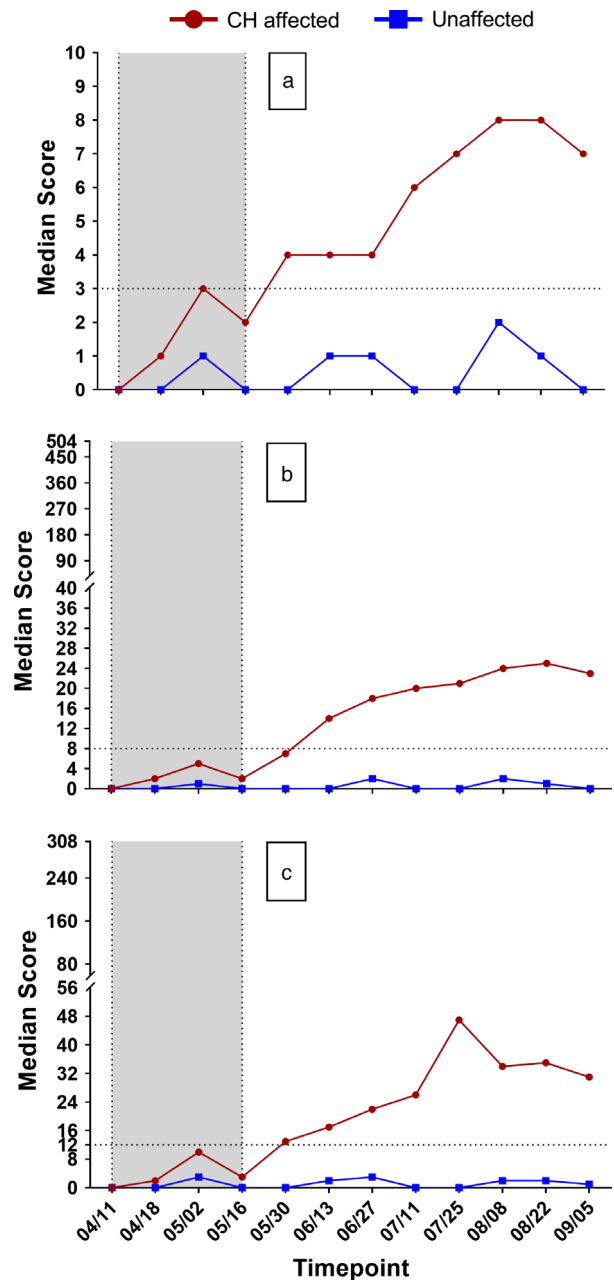


Figure 1. Median scores for CH affected horses ($n = 8$; red line) and unaffected horses ($n = 13$; blue line) for each scoring system (top to bottom, a–c) during the observation period.

The grey area corresponds to the time without *Culicoides* exposure. For the remaining observation period, *Culicoides* were present in the environment of the horses. Dotted lines represent the allergic cut off values determined by ROC analysis. Y-axes represent the total possible range of scores for each system and have broken axes to display maximum attainable score. CH affected, *Culicoides* hypersensitive; Unaffected, not *Culicoides* hypersensitive.

were correctly classified (i.e. CH affected horses were correctly defined as affected and control horses were correctly defined as unaffected). Using the median of the cut-off scores across all time points, scores ≥ 3 , 8 and 12 were defined as the overall cut-off points that supported the classification of CH by scoring systems A, B and C, respectively (Table 2).

The ROC-AUC analysis also was used to determine the discriminatory ability of each system: the system's ability



Figure 2. Photographs of clinical lesions representing the most commonly affected locations in this study demographic. Images represent moderate to severely affected horses. Lesions affecting the (a) ventrum, (b) chest, (c) face and (d) tail.

to correctly classify horses that were CH affected or unaffected. All three systems demonstrated good accuracy (high discriminatory ability) with median AUCs across all time points of >0.80 (System A = 0.85, System B = 0.87 and System C = 0.87; Table 2).

Using these objectively determined cross-seasonal allergic cut-off points, horses' classifications were then assessed for each scoring system at each time point. Figure 3 illustrates which horses were correctly or incorrectly classified, and groups the horses into CH affected and unaffected. These groupings reveal that the same horses were incorrectly classified by the scoring systems at similar time points. Additionally, the figure demonstrates that the highest number of correctly classified horses occurred in the peak *Culicoides* allergic season, August to September.

Scoring system agreement

Correlation of summed scores between systems for each time point was analyzed by Spearman's rho calculations (Table 3). The median (range) of Spearman's rho across all eight observations between May and September was as follows: System A compared to system B was 0.97 (0.93–1.0); System A compared to System C was 0.96 (0.94–1.0); and System B compared to System C was 0.99 (0.99–1.0), indicating strong correlations for all comparisons.

Agreement between classifications for each time point was analyzed using Cohen's kappa as a measurement of agreement beyond chance (Table 3). The median (range) kappa values across all eight observations between May and September were as follows: System A compared to System B was 0.77 (0.56–1); System A compared to

Table 2. Logistic regression analysis ROC-AUC for each of the three scoring systems for *Culicoides* hypersensitivity

Time point	Scoring system					
	A		B		C	
	AUC	Cut-off	AUC	Cut-off	AUC	Cut-off
5/30/17	0.802	1	0.838	1	0.854	6
6/13/17	0.688	5	0.698	10	0.708	24
6/27/17	0.823	2	0.870	17	0.865	19
7/11/17	0.859	1	0.875	19	0.856	25
7/25/17	0.917	4	0.942	6	0.932	8
8/8/17	0.833	4	0.833	16	0.839	10
8/22/17	0.865	4	0.885	4	0.922	6
9/5/17	0.927	2	0.927	2	0.943	11
Median	0.846	3	0.873	8	0.865	11.5
Range	0.688–0.927	1–5	0.698–0.942	1–19	0.708–0.943	2–25

Scoring systems A–C are described in detail in Figures S1–S3.

Clinical scoring allergic cut-off points are reported for each sampling date.

In addition, the median (range) is presented across time points.

Only the eight time points in season when clinical signs occurred were considered.

AUC, area under the curve; ROC, receiver operating characteristic.

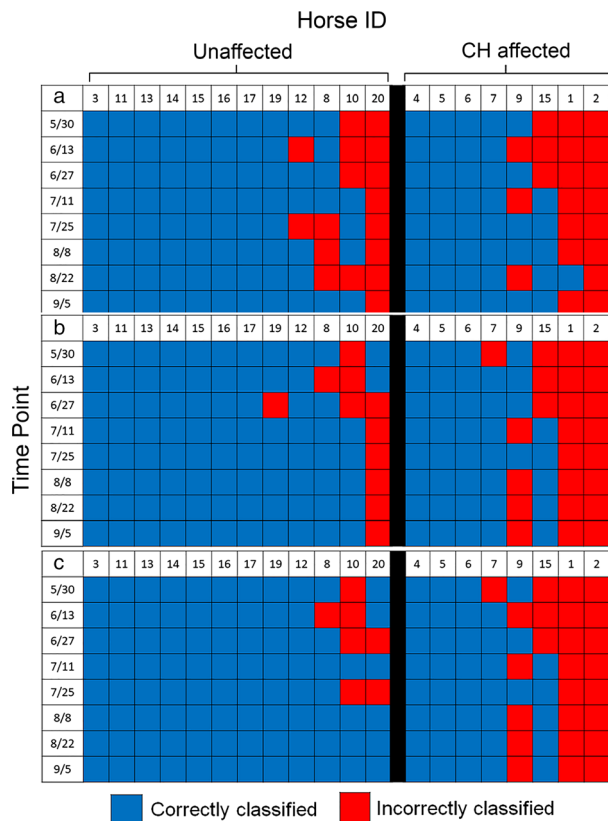


Figure 3. Classification of individual horses ($n = 20$, eight CH affected and 12 unaffected) for each time point and each scoring system based on the median cut-off identified by ROC-AUC analysis. Scoring systems: a to c, top to bottom. Blue squares represent horses that were classified correctly and red squares represent horses that were classified incorrectly. Horses are listed as individuals under their horse ID, are grouped into unaffected and CH affected, and are arranged to group the incorrectly classified horses. CH affected, *Culicoides* hypersensitive; Unaffected, not *Culicoides* hypersensitive.

System C was 0.73 (0.58–0.89); and System B compared to System C was 0.88 (0.78–1.0), indicating substantial agreement for all comparisons.

Discussion

The three scoring systems investigated in this study had excellent discriminatory ability as well as significant agreement with each other, making them good candidates for consideration in the development of a standardized clinical scoring system. The natural *Culicoides* exposure experienced by this research herd from May to September allowed confirmation of the characteristic seasonality of CH with clinical lesions peaking in the warmest summer months, as described previously.⁷ The ability of each of the three scoring systems to correctly classify a horse's CH status was generally good throughout the entire season as evidenced by high ROC-AUC values (median > 0.85). However, peak lesion dates also coincided with the highest accuracy and smallest number of horses incorrectly classified by the scoring systems. Figure 3 demonstrates that there was a notable pattern in which horses were incorrectly classified by the scoring systems. Each system incorrectly classified the same horses throughout the sampling period. For example, Horse 20, an unaffected control, had significant loss of mane with associated excoriations due to frequent attempts to eat grass under the wooden fence. This horse was routinely incorrectly classified by systems A and B, and to a much lesser extent System C. In addition, CH-affected horses 1 and 2 were incorrectly classified as "unaffected" by all scoring systems at virtually all time points due to their very mild clinical lesions. This may have been due to a change in their allergic status or the fact that the mild clinical lesions were not detected by the proposed allergic cut-off points used herein. These patterns highlight the fact that clinical scoring systems are inaccurate in the face of very mild clinical lesions and that the entire clinical picture of the horse and its behaviours must be taken into consideration when using them. Therefore, the CH scoring systems should be used judiciously when few lesions are present outside of peak allergy season.²

Very strong correlation of scores between systems was found, indicating that the observer's scores agreed

Table 3. Individual Spearman's rho calculations and Cohen's kappa calculations comparing systems to one another for each sampling date, as well as median (range) across time points

Time point	Correlation A–B	Correlation A–C	Correlation B–C	Kappa A–B	Kappa A–C	Kappa B–C
30/5/17	0.972	0.962	0.998	0.765	0.765	1.000
13/6/17	0.929	0.936	0.992	0.560	0.659	0.886
27/6/17	0.961	0.956	0.991	0.894	0.886	0.783
11/7/17	0.979	0.973	0.995	1.000	0.875	0.875
25/7/17	0.976	0.962	0.989	0.700	0.700	1.000
8/8/17	0.976	0.968	0.993	0.783	0.667	0.875
22/8/17	0.956	0.949	0.993	0.688	0.579	0.875
5/9/17	0.999	0.996	0.997	0.886	0.765	0.875
Median	0.974	0.962	0.993	0.774	0.7325	0.875
Range	0.929–0.999	0.936–0.996	0.989–0.998	0.560–1.000	0.579–0.886	0.783–1.000

Only the eight time points in season when clinical signs occurred were considered.

well with one another from system to system. This was demonstrated by Spearman's rho ranging from 0.96 to 0.99, where perfect correlation is reported as a 1.0. All three clinical scoring systems also demonstrated substantial agreement with one another for classification of CH status as validated in the Cohen's kappa ranging from 0.73 to 0.88. Kappa values of 0.61–0.80 are considered substantial and 0.81–1.00 almost perfect agreement.^{25,26} This excellent correlation and agreement supports the use of all three systems for future development of a standardized clinical scoring system.

The Icelandic horses residing in this research herd provided an unique clinical situation for an initial comparison of the three scoring systems. All horses lived in the same environment, received the same diet, vaccinations and deworming schedules, and shared the same risk of exposure to the local fly and midge populations. This unique situation would be impossible to achieve with client-owned horses at different locations and with multiple environmental variables that might confound comparisons. However, the small number of horses with CH in the herd ($n = 8$) and the use of a single breed located at one site may have influenced the results. The most common locations for lesion development included the face, ventral midline, mane, tail and chest (Figure 2). Lesions on the dorsum, other than the mane and tail, which have been commonly reported in other countries^{10–15} were not noted in the present study. This lesion variability was likely to have been associated with specific *Culicoides* species having preferred landing sites, as well as local environmental influences.¹³ Additionally, a single observer in this preliminary study was chosen to reduce variability and allow for a better direct comparison of scoring systems. Moving forward, these systems should be compared in various breeds and geographical locations, using multiple observers with variable levels of practice experience in equine dermatology, to identify areas where repeatability may be compromised.

In small animal dermatology, the Canine Atopic Dermatitis Extent and Severity Index (CADESI) and Canine Atopic Dermatitis Lesion Index (CADLI) scoring systems have been developed to standardize the evaluation of atopic dogs in clinical trials.^{27–31} In the most recent iterations, the use of fewer data points has been reported to be effective in promoting efficiency and minimizing inter-observer variation.^{30,31} The present study also supports the use of fewer data points, which is evidenced by the

high discriminatory ability and excellent agreement of scoring systems B and C with the simpler System A. System A was the most efficient system to use, taking approximately 5 min per horse to complete, and CH-affected horses often achieved the total maximum score of 10. Despite being the most efficient system, it is conceivable that System A would not be able to discern differences in the severity of affected horses beyond a certain clinical point. Additionally, System A may not be ideal when quantifying response to treatment if subtle changes in clinical lesions are considered noteworthy. Systems B and C took much longer to score and never approached their maximum total scores despite the fact that CH-affected horses in this study population had severe clinical lesions in multiple locations. This suggests that these systems contain excessive categories, which may lead to decreased efficiency.

It was not the aim of the current study to determine which scoring system should be used moving forward towards a standardized system. This choice requires further studies evaluating each system, as well as a dialogue amongst experts on CH and must take into consideration study parameters such as the total number of clinical scoring events, number of horses in the study, desired details on the description of clinical lesions, and number and experience of observers performing the clinical scoring. Each system assessed in this study had notable limitations. On the one hand, systems A and B gave minimal guidance regarding how to score a lesion's severity, which may lead to increased interobserver variability. System C, on the other hand, had very detailed instructions regarding how to score lesions but was cumbersome with regard to how long it took to score an individual horse. In moving towards adapting a standardized clinical scoring system, further studies are required to assess these limitations and provide data regarding how each of these systems performs in different situations.

Culicoides hypersensitivity remains an allergic condition that is diagnosed based on a composite of clinical parameters including clinical signs, distinctive seasonality of lesions and response to *Culicoides* avoidance.^{2,3} Although CH scoring systems cannot be used as stand-alone diagnostic test, they are valuable in that they provide a method for numeric quantification of the allergic response. This is particularly useful in research when results across study populations and responses to therapeutic interventions are quantified and compared.

However, the numerical cut-off points used for statistical comparisons of the three scoring systems in the present study should not be used to diagnose CH. If allergic cut-offs are to be used for evaluation of clinical trials in the future, further validation in independent populations of horses during seasons of *Culicoides* activity in various regions is recommended.

In conclusion, the results of this study support the use of clinical scoring systems to aid in the quantification of clinical signs associated with CH and to more objectively monitor response to therapeutic interventions. Evaluation of new pharmacological or immunotherapeutic options for CH will benefit from a validated scoring system that permits comparison of results between study populations. The three scoring systems compared here are good candidates for further development of a standardized tool.

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Figure S1. Scoring System A (courtesy of Bettina Wagner).

Figure S2. Scoring System B. According to and modified from Geiben.³²

Figure S3. Scoring System C. According to and modified from Fettelschoss-Gabriel.²²

Résumé

Contexte – L'hypersensibilité aux piqûres de culicoïdes (CH), dermatite allergique saisonnière intensément prurigineuse, est une maladie allergique fréquente touchant les chevaux dans le monde entier. Aucun système de notation n'est à ce jour validé pour la quantification des signes cliniques associés à CH.

Objectifs – Déterminer (i) le meilleur seuil de trois systèmes de notation, (ii) évaluer la précision de chaque système comparé au diagnostic clinique d'un vétérinaire expérimenté et (iii) déterminer la concordance entre les systèmes.

Sujets – Des chevaux islandais ($n = 20$); huit avec CH et 12 sains, issus d'un troupeau de recherche ne recevant aucun traitement pour dermatite allergique.

Matériels et méthodes – Les scores lésionnels ont été enregistrés deux fois par semaine d'avril à septembre avec trois systèmes de notation (A, B et C) par un seul investigateur initialement aveugle au statut CH. Les analyses de régression logistique pour chaque point ont été utilisées pour déterminer le statut approprié pour classer en CH. Le rho de Spearman et le kappa de Cohen ont été calculés pour analyser respectivement la corrélation entre les scores et la concordance de la catégorisation de CH entre les systèmes.

Résultats – Le meilleur des scores seuils des systèmes A, B et C étaient respectivement trois, huit et 12. Pour chaque système, les aires médianes sous la courbe (>0.85) étaient excellentes et la capacité de discrimination pour une classification correcte du statut CH était forte. Une corrélation excellente entre les scores pour chaque système (rho de Spearman > 0.96) et un accord inter système excellent pour la catégorisation de CH (kappa ≥ 0.73) ont été trouvés parmi la notation de chaque temps de mesure.

Conclusions et importance clinique – Les résultats soutiennent l'utilisation de ces systèmes de notation comme modèle pour de futures standardisations de système de notation cliniques de CH.

Resumen

Introducción – la hipersensibilidad a los culicoides (CH), una dermatitis alérgica intensamente pruriginosa y estacional, es una enfermedad alérgica común que afecta a los caballos en todo el mundo. Actualmente, no existe un sistema de valoración clínica validado para la cuantificación de los signos clínicos asociados con CH.

Objetivos – (i) determinar el mejor valor de corte de tres sistemas de puntuación, (ii) probar la precisión de cada sistema en comparación con el diagnóstico clínico de un veterinario experimentado y (iii) evaluar la equivalencia entre los sistemas.

Animales – caballos islandeses ($n = 20$); ocho con CH y 12 no afectados, de un grupo de caballos de investigación que no recibían tratamientos para la dermatitis alérgica.

Métodos y materiales – los valores de las lesiones se registraron cada dos semanas desde abril hasta septiembre con tres sistemas de calificación clínica (A, B y C) por un solo observador inicialmente desconocedor del estado de CH. Se utilizaron análisis de regresión logística separados para cada punto de tiempo para determinar los valores de corte apropiados para la clasificación de CH. Se calcularon el valor rho de Spearman y la kappa de Cohen para analizar la correlación de valores y la equivalencia en la categorización de CH entre sistemas, respectivamente.

Resultados – se determinó que los mejores valores de corte de alergia para los sistemas A, B y C eran tres, ocho y 12, respectivamente. Para todos los sistemas, las áreas medianas bajo la curva (> 0.85) fueron excelentes y la capacidad discriminatoria para clasificar correctamente el estado de CH fue elevada. Se determinó una excelente correlación entre los valores de cada sistema (rho de Spearman > 0.96) y una excelente equivalencia entre sistemas para la categorización de CH (kappa ≥ 0.73) en los puntos de tiempo valorados.

Conclusión e importancia clínica – los resultados respaldan el uso de estos sistemas de puntuación como bases para la futura estandarización de un sistema de valoración clínica de la CH.

Zusammenfassung

Hintergrund – Die *Culicoides* Hypersensibilität (CH), eine höchst juckende und saisonale allergische Dermatitis, ist eine häufige allergische Erkrankung, die Pferde weltweit betrifft. Zurzeit gibt es kein validiertes Bewertungssystem für die Quantifizierung einer klinischen Erkrankung, die mit CH zusammenhängt.

Ziele – (i) Bestimmung des besten Cut-Off Punktes bei drei Bewertungssystemen, (ii) Untersuchung der Genauigkeit eines jeden Systems im Vergleich zur klinischen Diagnose eines erfahrenen Tierarztes und (iii) Erfassung der Übereinstimmung zwischen den Systemen.

Tiere – Isländpferde (n = 20); acht mit CH und 12 nicht betroffene Tiere aus einer Versuchsherde, die keine Behandlungen für allergische Dermatitis erhielten.

Methoden und Materialien – Die Grade der Hautveränderungen wurden zweimal wöchentlich von April bis September mit drei klinischen Bewertungssystemen (A, B und C) durch einen einzigen, anfangs dem CH Status gegenüber geblindeten Untersucher, festgehalten. Eine separate logistische Regressionsanalyse wurde für jeden Zeitpunkt verwendet, um entsprechende Cut-off Punkte für eine CH Klassifizierung zu bestimmen. Spearman's RHO und Cohen's Kappa wurden kalkuliert, um die Korrelation der Werte bzw. die Übereinstimmung der CH Kategorisierung zwischen den Systemen zu bestimmen.

Ergebnisse – Die besten allergischen Cut-Off Werte für die Systeme A, B bzw. C wurden bei drei, acht bzw. 12 festgelegt. Für alle Systeme waren die Medianflächen unter der Kurve ($>0,85$) exzellent und die charakterisierende Fähigkeit, um CH Status korrekt zu klassifizieren, war stark. Es wurde bei allen Bewertungspunkten eine exzellente Korrelation zwischen den Werten für jedes System (Spearman's RHO $> 0,96$) und eine exzellente Übereinstimmung zwischen den Systemen für eine CH Kategorisierung ($\text{kappa} \geq 0,73$) festgestellt.

Schlussfolgerungen und klinische Bedeutung – Die Ergebnisse unterstützen die Verwendung dieser Bewertungssysteme als Vorlagen für eine zukünftige Standardisierung eines klinischen Bewertungssystems für CH.

要約

背景 – 激しい掻痒性および季節性アレルギー性皮膚炎である *Culicoides hypersensitivity* (CH) は、世界中の馬に罹患する一般的なアレルギー性疾患である。現在、CHに関連した臨床徴候の定量化に対する有効な臨床採点システムはない。

目的 – 本研究の目的は、(i) 3つのスコアリングシステムの最良のカットオフポイントを決定すること、(ii) 経験豊富な獣医師の臨床診断と比較したときの各システムの精度を調査すること、および (iii) システム間の一致を評価すること、である。

被験動物 – アイスランドの馬 (n = 20): アレルギー性皮膚炎の治療を受けていない研究群から CH に罹患した馬 12 頭および罹患していない 8 頭。

材料と方法 – 病変スコアは 4 月から 9 月まで隔週で 3 つの臨床スコアリングシステム (A、B および C) を用いて一人の観察者により最初は CH 状態を盲検化して観察された。各時点について別々のロジスティック回帰分析を用いて、CH 分類の適切なカットオフを決定した。スピアマンの q とコーエンの j を、それぞれシステム間のスコアの相関と CH 分類の一致を分析するために計算した。

結果 – システム A、B および C の最良のアレルギーカットオフスコアを、それぞれ 3、8 および 12 と決定した。各系について、曲線下面積の中央値 ($> 0,85$) は優れており、CH 状態を正しく分類する識別能力は強かった。各システムのスコア間の優れた相関関係 (Spearman の $q > 0,96$) と CH 分類の優れたシステム間一致 ($\text{kappa} \geq 0,73$) がスコアリング時点で見つかった。

結論および臨床的重要性 – 結果は、CH 臨床スコアリングシステムの将来の標準化のためのテンプレートとしてこれらのスコアリングシステムの使用を支持している。

摘要

背景 – 库蠓过敏 (CH) 是一种严重瘙痒、季节性和过敏性的皮炎, 是全世界的马均易感的常见过敏性疾病。目前, 尚无有效的临床评分系统来量化 CH 的临床病征。

目的 – (i) 确定三个评分系统的最佳分界点; (ii) 与经验丰富的兽医作出的临床诊断相比较, 测试每个系统的准确性; (iii) 评估系统之间的一致性。

动物 – 未接受过敏性皮炎治疗的冰岛马 (n = 20): 其中 8 匹患有 CH, 12 匹未患病。

方法和材料 – 从 4 月到 9 月, 由最初对 CH 状态不知情的独立观察者以三种临床评分系统 (A, B 和 C) 记录病变评分, 每两周记录一次。对每个时间点分别进行逻辑回归分析, 以确定 CH 分类的适当分界点。分别用斯皮尔曼等级相关系数和科恩 kappa 系数计算分析系统之间的得分相关性和 CH 分类的一致性。

结果 – 系统 A、B 和 C 的最佳过敏分界值分别为 3、8 和 12。对于每个系统, 曲线下的中位数区域 ($> 0,85$) 均良好, 对 CH 状态分类的辨别能力很强。在评分时间点内发现, 每个系统的得分 (斯皮尔曼等级相关系数 $> 0,96$) 显著相关, CH 分类的系统间一致性 ($\text{kappa} \geq 0,73$) 显著相关。

结论和临床意义 – 结果支持使用这些评分系统未来作为标准化 CH 临床评分系统的模板。

Resumo

Contexto – A hipersensibilidade por *Culicoides* (CH), uma dermatite alérgica sazonal intensamente pruriginosa, é uma doença alérgica comum que afeta cavalos pelo mundo. Atualmente, não há um sistema de escore clínico validado para a quantificação dos sinais clínicos associados à CH.

Objetivos – (i) determinar o melhor ponto de corte de três sistemas de escore, (ii) testar a acurácia de cada sistema comparado ao diagnóstico clínico de um veterinário experiente e (iii) avaliar a concordância entre os sistemas.

Animais – Cavalos islandeses (n = 20); oito com CH e 12 não afetados, de um rebanho experimental, que não estavam recebendo nenhum tratamento para dermatite alérgica.

Métodos e materiais – Os escores de lesão foram registrados a cada duas semanas de abril a setembro com três sistemas de escore clínico (A, B e C) por um único observador inicialmente cego ao status de CH. Análises de regressão logística separadas para cada tempo experimental foram utilizadas para determinar os pontos de corte apropriados para a classificação de CH. O rho de Spearman e o Kappa de Cohen foram calculados para analisar a correlação dos escores e a concordância da categorização de CH entre os sistemas, respectivamente.

Resultados – Os melhores escores alérgicos para os sistemas A, B e C foram três, oito e 12, respectivamente. Para cada sistema a mediana das áreas sob a curva ($>0,85$) foi excelente e a habilidade discriminatória de classificação correta de CH foi alta. Observou-se excelente correlação entre os escores para cada sistema (Rho de Spearman $> 0,96$) e excelente concordância entre sistemas para categorização de CH (kappa $\geq 0,73$) ao longo dos tempos experimentais.

Conclusão e importância clínica – Os resultados corroboram com o uso dos três sistemas de escore como modelos para uma futura padronização de um sistema de escore para CH.

Supporting Information

Figure S1. Scoring system A (courtesy of Bettina Wagner).

System A			Date:				
			Weather:				
			Flies in enviro:	None	Few	Many	
Name	ID#	Pruritus	Alopecia	Skin irritation	Comment		
Pruritus		Alopecia		Skin irritation			
0 no scratching		0 none		0 no skin irritation			
1 mild, mane OR tail		1 few broken hairs, 1 location		1 mild dermatitis, 1 location			
2 moderate, mane and/or tail		2 several locations broken hair		2 moderate, several locations			
3 intense mane and tail		3 moderate hair loss mane OR tail		3 severe dermatitis with skin lesions			
		4 severe hair loss, mane and tail					

Figure S2. Scoring system B. According to and modified after Geiben

Geiben T. Studies on summer eczema and on the influence of the immunomodulator Baypamun N® on type I allergy in horses. Doctoral thesis 2003. Veterinary School Hannover, Germany - <https://dnb.info/969238762/34> Accessed 03/07/2019

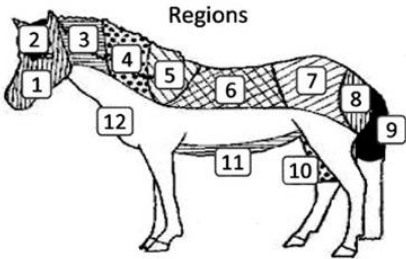
Evaluation of Skin						Scoring Comparison Study	
Horse's Name		Horse Number		Date			
				Coding 0 not present 1 very mild 2 mild 3 mild to moderate 4 moderate 5 moderate to severe 6 severe			
Region	Wheals	Papules	Broken Hairs	Alopecia	Crusts, Scabing	Blood, Exudate	Purulence
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Photographs taken?							
Remarks (weather, <i>Culicoides</i> , etc...)							
Visit Date (DD-MMM-YYYY)		- -		Signature			

Figure S3. Scoring system C. According to and modified from Fettelschoss-Gabriel et al. 2018

Fettelschoss-Gabriel A, Fettelschoss V, Olomski F *et al.* Active vaccination against Interleukin-5 as long-term treatment for insect bite hypersensitivity in horses. *Allergy* 2018; 142: 1,194-1,205.

[SCORE SHEET LESION GRADING]

1

STUDY TITLE _____

STUDY ID _____

DATE, PLACE _____

OWNER _____

HORSE NAME / PATIENT ID _____

Points are given for each summer eczema site. Every site is judged for intensity on location, size/diameter, blood, hairloss, scales, crust and lichenification. Per site intensities are graded from 1 to maximal 4 points. Total points is sum of all points. For more information, see page 4.

TAIL	POINTS				
LOCATION ☐	UP ☐	MIDDLE ☐	DOWN ☐	LIGHT ☐	STRONG ☐
SIZE / DIAMETER	1 ☐	2 ☐	3 ☐	4 ☐	0
BLOOD	1 ☐	2 ☐	3 ☐	4 ☐	0
HAIRLOSS	1 ☐	2 ☐	3 ☐	4 ☐	0
SCALES	1 ☐	2 ☐	3 ☐	4 ☐	0
CRUST	1 ☐	2 ☐	3 ☐	4 ☐	0
LICHENIFICATION / SWELLING	1 ☐	2 ☐	3 ☐	4 ☐	0

MANE	POINTS				
LOCATION ☐	UP ☐	MIDDLE ☐	DOWN ☐	LIGHT ☐	STRONG ☐
SIZE / DIAMETER	1 ☐	2 ☐	3 ☐	4 ☐	0
BLOOD	1 ☐	2 ☐	3 ☐	4 ☐	0
HAIRLOSS	1 ☐	2 ☐	3 ☐	4 ☐	0
SCALES	1 ☐	2 ☐	3 ☐	4 ☐	0
CRUST	1 ☐	2 ☐	3 ☐	4 ☐	0
LICHENIFICATION / SWELLING	1 ☐	2 ☐	3 ☐	4 ☐	0

BELLY	POINTS				
LOCATION ☐	UP ☐	MIDDLE ☐	DOWN ☐	LIGHT ☐	STRONG ☐
SIZE / DIAMETER	1 ☐	2 ☐	3 ☐	4 ☐	0
BLOOD	1 ☐	2 ☐	3 ☐	4 ☐	0
HAIRLOSS	1 ☐	2 ☐	3 ☐	4 ☐	0
SCALES	1 ☐	2 ☐	3 ☐	4 ☐	0
CRUST	1 ☐	2 ☐	3 ☐	4 ☐	0
LICHENIFICATION / SWELLING	1 ☐	2 ☐	3 ☐	4 ☐	0

[SCORE SHEET LESION GRADING]

3

LEGS	POINTS				
LOCATION ☐	UP ☐	MIDDLE ☐	DOWN ☐	LIGHT ☐	STRONG ☐
SIZE / DIAMETER	1 ☐	2 ☐	3 ☐	4 ☐	0
BLOOD	1 ☐	2 ☐	3 ☐	4 ☐	0
HAIRLOSS	1 ☐	2 ☐	3 ☐	4 ☐	0
SCALES	1 ☐	2 ☐	3 ☐	4 ☐	0
CRUST	1 ☐	2 ☐	3 ☐	4 ☐	0
LICHENIFICATION / SWELLING	1 ☐	2 ☐	3 ☐	4 ☐	0

CROUP	POINTS				
LOCATION ☐	UP ☐	MIDDLE ☐	DOWN ☐	LIGHT ☐	STRONG ☐
SIZE / DIAMETER	1 ☐	2 ☐	3 ☐	4 ☐	0
BLOOD	1 ☐	2 ☐	3 ☐	4 ☐	0
HAIRLOSS	1 ☐	2 ☐	3 ☐	4 ☐	0
SCALES	1 ☐	2 ☐	3 ☐	4 ☐	0
CRUST	1 ☐	2 ☐	3 ☐	4 ☐	0
LICHENIFICATION / SWELLING	1 ☐	2 ☐	3 ☐	4 ☐	0

OTHER	POINTS				
LOCATION ☐	UP ☐	MIDDLE ☐	DOWN ☐	LIGHT ☐	STRONG ☐
SIZE / DIAMETER	1 ☐	2 ☐	3 ☐	4 ☐	0
BLOOD	1 ☐	2 ☐	3 ☐	4 ☐	0
HAIRLOSS	1 ☐	2 ☐	3 ☐	4 ☐	0
SCALES	1 ☐	2 ☐	3 ☐	4 ☐	0
CRUST	1 ☐	2 ☐	3 ☐	4 ☐	0
LICHENIFICATION / SWELLING	1 ☐	2 ☐	3 ☐	4 ☐	0

OTHER	POINTS				
LOCATION ☐	UP ☐	MIDDLE ☐	DOWN ☐	LIGHT ☐	STRONG ☐
SIZE / DIAMETER	1 ☐	2 ☐	3 ☐	4 ☐	0
BLOOD	1 ☐	2 ☐	3 ☐	4 ☐	0
HAIRLOSS	1 ☐	2 ☐	3 ☐	4 ☐	0
SCALES	1 ☐	2 ☐	3 ☐	4 ☐	0
CRUST	1 ☐	2 ☐	3 ☐	4 ☐	0
LICHENIFICATION / SWELLING	1 ☐	2 ☐	3 ☐	4 ☐	0

[SCORE SHEET LESION GRADING]

2

WITHERS	POINTS				
LOCATION ☐	UP ☐	MIDDLE ☐	DOWN ☐	LIGHT ☐	STRONG ☐
SIZE / DIAMETER	1 ☐	2 ☐	3 ☐	4 ☐	0
BLOOD	1 ☐	2 ☐	3 ☐	4 ☐	0
HAIRLOSS	1 ☐	2 ☐	3 ☐	4 ☐	0
SCALES	1 ☐	2 ☐	3 ☐	4 ☐	0
CRUST	1 ☐	2 ☐	3 ☐	4 ☐	0
LICHENIFICATION / SWELLING	1 ☐	2 ☐	3 ☐	4 ☐	0

FLANK	POINTS				
LOCATION ☐	UP ☐	MIDDLE ☐	DOWN ☐	LIGHT ☐	STRONG ☐
SIZE / DIAMETER	1 ☐	2 ☐	3 ☐	4 ☐	0
BLOOD	1 ☐	2 ☐	3 ☐	4 ☐	0
HAIRLOSS	1 ☐	2 ☐	3 ☐	4 ☐	0
SCALES	1 ☐	2 ☐	3 ☐	4 ☐	0
CRUST	1 ☐	2 ☐	3 ☐	4 ☐	0
LICHENIFICATION / SWELLING	1 ☐	2 ☐	3 ☐	4 ☐	0

FACE	POINTS				
LOCATION ☐	UP ☐	MIDDLE ☐	DOWN ☐	LIGHT ☐	STRONG ☐
SIZE / DIAMETER	1 ☐	2 ☐	3 ☐	4 ☐	0
BLOOD	1 ☐	2 ☐	3 ☐	4 ☐	0
HAIRLOSS	1 ☐	2 ☐	3 ☐	4 ☐	0
SCALES	1 ☐	2 ☐	3 ☐	4 ☐	0
CRUST	1 ☐	2 ☐	3 ☐	4 ☐	0
LICHENIFICATION / SWELLING	1 ☐	2 ☐	3 ☐	4 ☐	0

EARS	POINTS				
LOCATION ☐	UP ☐	MIDDLE ☐	DOWN ☐	LIGHT ☐	STRONG ☐
SIZE / DIAMETER	1 ☐	2 ☐	3 ☐	4 ☐	0
BLOOD	1 ☐	2 ☐	3 ☐	4 ☐	0
HAIRLOSS	1 ☐	2 ☐	3 ☐	4 ☐	0
SCALES	1 ☐	2 ☐	3 ☐	4 ☐	0
CRUST	1 ☐	2 ☐	3 ☐	4 ☐	0
LICHENIFICATION / SWELLING	1 ☐	2 ☐	3 ☐	4 ☐	0

[SCORE SHEET LESION GRADING]

4

SHEATH / UDDER	POINTS			
Sheath	GRADE 1 ☐	GRADE 2 ☐	GRADE 3 ☐	GRADE 4 ☐
Udder	GRADE 1 ☐	GRADE 2 ☐	GRADE 3 ☐	GRADE 4 ☐
TOTAL POINTS	0			

NOTES

VETERINARY _____ RESEARCHER _____

LESION SCORING

For IBH symptom scoring, the location (tail, mane, belly, flank, face, ear, leg, and the like) where IBH lesions occur are recorded. Each location is divided into 3 parts: up, middle, down. Further according to the number of lesions, each location is classified into light and strong. Dependent on how many parts are affected (up / middle / down) and how many lesions per location are found (light / strong), 1 to 4 points can be scored (1 point = one part affected, lesion light; 4 points = all three parts affected, lesion strong). Moreover, these locations are classified for 6 further properties: size (diameter), blood, hair loss, scales, crust, and lichenification / swelling. For all these properties also 1 to 4 points can be scored. Size is divided into < 0.5 cm (1 point), 0.5 $\geq$ x > 1 cm (2 points), 1 $\geq$ x > 2 cm (3 points), and $\geq$ 2 cm (4 points). Blood is divided into intact epidermis (1 point), mild (2 points), moderate (3 points), and severe (4 points). Hair loss is divided into mild (1 point), moderate (2 points), severe (3 points), and no hair (4 points). Scales is divided into none (1 point), tiny, few (2 points), moderate, mid-size (3 points), and many, big (4 points). Crust is divided into none (1 point), tiny (2 points), half (3 points), and total (4 points). Lichenification and/or swelling is divided into none (1 point), mild (2 points), moderate (3 points), and severe (4 points). Additionally, if sheath or udder is swollen, minimally 5 or maximally 20 points can be scored: grade 1 (5 points), grade 2 (10 points), grade 3 (15 points), and grade 4 (20 points). Finally, all points are added up and are the IBH symptom score.