

# Evaluation of Coughing and Nasal Discharge as Early Indicators for An Increased Risk to Develop Equine Recurrent Airway Obstruction (RAO)

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**Background:** It is often assumed that horses with mild respiratory clinical signs, such as mucous nasal discharge and occasional coughing, have an increased risk of developing recurrent airway obstruction (RAO).

**Hypothesis:** Compared to horses without any clinical signs of respiratory disease, those with occasional coughing, mucous nasal discharge, or both have an increased risk of developing signs of RAO (frequent coughing, increased breathing effort, exercise intolerance, or a combination of these) as characterized by the Horse Owner Assessed Respiratory Signs Index (HOARSI 1–4).

**Animals:** Two half-sibling families descending from 2 RAO-affected stallions (n = 65 and n = 47) and an independent replication population of unrelated horses (n = 88).

**Methods:** In a retrospective cohort study, standardized information on occurrence and frequency of coughing, mucous nasal discharge, poor performance, and abnormal breathing effort—and these factors combined in the HOARSI—as well as management factors were collected at intervals of 1.3–5 years.

**Results:** Compared to horses without clinical signs of respiratory disease (half-siblings 7%; unrelated horses 3%), those with mild respiratory signs developed clinical signs of RAO more frequently: half-siblings with mucous nasal discharge 35% ( $P < .001$ , OR: 7.0, sensitivity: 62%, specificity: 81%), with mucous nasal discharge and occasional coughing 43% ( $P < .001$ , OR: 9.9, sensitivity: 55%, specificity: 89%); unrelated horses with occasional coughing: 25% ( $P = .006$ , OR = 9.7, sensitivity: 75%, specificity: 76%).

**Conclusions and Clinical importance:** Occasional coughing and mucous nasal discharge might represent an increased risk of developing RAO.

**Key words:** HOARSI; IAD; Pulmonary; Questionnaire.

Both lay people and veterinarians often assume that horses with mild respiratory signs such as occasional coughing, mucous nasal discharge, or both—clinical signs associated with inflammatory airway disease (IAD)<sup>1</sup>—have an increased risk of developing recurrent airway obstruction (RAO) when compared to horses without these signs.<sup>2</sup> To our knowledge, there is no published evidence for this assumption. The risk for a horse with IAD of developing RAO and the relationship between the 2 conditions are still unknown.<sup>3,4</sup> As a result of a workshop on respiratory disease, the American Association of Equine Practitioners concluded that determining whether IAD is a precursor to RAO is a “priority question”.<sup>5</sup>

IAD is a common, relatively mild respiratory disease, affecting horses of all ages.<sup>1,6</sup> RAO, in contrast, affects middle-aged to older horses and provokes more severe respiratory signs. A strong genetic basis was shown for RAO<sup>7–9</sup> and hay feeding is the most important environmental factor for its development<sup>4,10,11</sup> and exacerbation.<sup>12,13</sup>

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## Abbreviations:

BALF	bronchoalveolar lavage fluid
CI	confidence interval
F1, F2	members of a high-incidence RAO half-sibling family
HOARSI	Horse Owner Assessed Respiratory Signs Index
IAD	inflammatory airway disease
OR	odds ratio
RAO	recurrent airway obstruction

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IAD and RAO can be differentiated based on clinical signs combined with ancillary diagnostics, such as cytologic evaluation of bronchoalveolar lavage fluid (BALF) and specialized pulmonary function testing.<sup>1</sup> Recently, several questionnaire-based scoring systems for lower airway disease in horses have been developed, ie, the risk screening questionnaire,<sup>14</sup> the HOARSI-system,<sup>11</sup> and the visual analog scale.<sup>15</sup> The Horse Owner Assessed Respiratory Signs Index (HOARSI) shows good repeatability and has been validated using standardized comprehensive clinical examination.<sup>11,16</sup> It is also the most extensively used of these scores, especially for genetic and epidemiologic studies, eg,<sup>7–9,17–20</sup>. The HOARSI is based on owner-observed clinical signs. Comprehensive validation demonstrated that HOARSI 3 and 4, characterized by frequent coughing, increased breathing effort and exercise intolerance reliably identify RAO-affected animals.<sup>16</sup> More mildly affected horses showing occasional coughing, mucous nasal discharge, or both are classified as HOARSI 2. HOARSI 1 indicates the absence of all of these clinical signs.

Symptom-scoring systems are also used as screening tools for the diagnosis of human asthma, for

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epidemiologic investigations, and also for clinical screening.<sup>21,22</sup> In equine medicine, there are only few published studies on the value of such scoring systems for clinical screening of horses with lower airway disease,<sup>14–16</sup> and none that have investigated their value in prognostication. The purpose of this study was to evaluate if scoring of owner-reported information can assist in formulating the prognosis of horses with mild respiratory clinical signs.

Coughing and nasal discharge are the most frequently and reliably recognized clinical signs of lower airway disease.<sup>11,15,23,24</sup> If occasional coughing and nasal discharge indicate an increased risk of later developing RAO, these mild clinical signs should be attributed more importance in the context of decisions on prophylactic measures (ie, environmental changes) to avoid development of RAO in susceptible animals. The specific aim of this study was therefore to investigate if the risk of developing RAO is increased in horses with occasional coughing, mucous nasal discharge, or both compared to horses without any respiratory clinical signs.

## Materials and Methods

### Study Design

Owners of horses in 2 half-sibling families were interviewed twice with an assessment interval of 1.3–3.8 years (mean = 2.3 years, 95% CI = 2.2–2.4 years). Owners of the independent replication population of unrelated Warmblood horses were also interviewed twice with a gap of 4.1–5 years (mean = 4.7 years, 95% CI = 4.7–4.7 years). Assessment intervals were significantly different between the 2 populations ( $P < .001$ ).

The following questions were investigated:

- Does the risk of developing RAO differ between the 2 half-sibling families?
- Are occasional coughing, nasal discharge, or both associated with an increased risk of developing RAO?
- Are signalment (age, sex, coat color) and environmental factors (bedding, time outdoors) associated with an increased risk for RAO?
- If clinical signs, signalment, or environmental factors have a significant influence on the development of RAO, what are the respective specificities and sensitivities?

### Horses and Classification

Two half-sibling families of direct descendants of 2 RAO-affected Warmblood stallions (F1,  $n = 65$  and F2,  $n = 47$ ) and an independent replication population of unrelated Warmblood horses ( $n = 88$ ) were graded according to HOARSI-1-4, from healthy to severely affected, as described in detail<sup>11</sup> and HOARSI 3 and 4 were classified as RAO-affected.<sup>11,16</sup> The replication population was a random sample from the register of the Swiss Equestrian Federation.<sup>17</sup> Feeding of hay during the whole study period was an inclusion criterion, as hay feeding is the most important environmental factor in the development of RAO.<sup>4,10,11</sup> Age (In the half-sibling group (F1 and F2 combined), the overall age range was 6–15 years, while the overall age range of the replication group was 5–24 years. For both populations, 2 age groups with approximately equal numbers of horses were then formed for statistical analysis. Half-sibling families, F1 and

F2 combined: younger group 6–9 years and older group 10–15 years of age; unrelated horses: younger group 5–12 years and older group 13–24 years of age), coat color (brown, other colors), time outdoors (0–1 hour, 1–multiple hours; 0–4 hours, 4–multiple hours), sex (stallions and geldings, mares), and clinical signs were recorded. Clinical signs—ie, mucous nasal discharge (absent, present), coughing (none, occasional, regular, frequent), increased breathing effort (absent, present), and performance (poor, adequate, good, excellent)—needed to be persistent for at least 2 months. The questionnaire also documented specific information on management and environmental factors, as previously described in detail.<sup>11</sup>

### Statistical Analyses

All information was categorized numerically for analyses with NCSS 2007 (NCSS Statistical Software, www.ncss.com). When Chi-square and Fishers exact tests showed significant results, specificities and sensitivities were calculated and univariable logistic regression analyses were performed to establish odds ratios (OR) with 95% confidence interval (CI). *T*-tests or, if the data were not normally distributed, Mann–Whitney *U* and Wilcoxon Rank-Sum Tests were used to investigate differences between the time intervals of the 2 assessments. Significance level was set at  $P \leq .05$ .

## Results

### Half-Sibling Families

**Difference between the 2 Half-sibling Families Regarding the Risk of Developing RAO.** No difference was found in the risk associated with developing RAO between the 2 half-sibling families ( $P = .79$ ; F1: 8 of 65 horses, 12%; F2: 5 of 47 horses, 11%). Thus, the 2 families were combined for further analyses. The intervals between the 2 assessments (time between first and second assessment in years) did not differ ( $P = .08$ ) between descendants of sire 1 (F1: mean = 2.2 years, 95% CI (95% confidence interval) = 2.1–2.4 years) and descendants of sire 2 (F2: mean = 2.4 years, 95% CI = 2.3–2.6 years).

**Effects of Occasional Coughing and Mucous Nasal Discharge on the Risk of Developing RAO.** Horses with occasional coughing in the first assessment did not develop RAO significantly more often (6 of 32 occasionally coughing horses, 19%) than healthy horses (5 of 71 healthy horses, 7%,  $P = .08$ ). Time intervals between the assessments did not differ between horses with occasional coughing (mean = 2.3 years, 95% CI = 2.1–2.5 years) at the first assessment and healthy horses (mean = 2.3 years, 95% CI = 2.1–2.4 years;  $P = .81$ ).

Horses with mucous nasal discharge in the first assessment developed RAO significantly more frequently (8 of 23 horses with mucous nasal discharge, 35%) than horses without any respiratory signs (7%;  $P < .001$ , OR = 7.0, 95% CI = 2.0–24.6 years, Table 2). Sensitivity of mucous nasal discharge as a predictive sign for RAO was 62%, and specificity was 81%. Time intervals did not differ ( $P = .42$ ) between horses with mucous nasal discharge (mean = 2.4 years, 95% CI = 2.2–2.6 years) and horses without clinical signs

(mean = 2.3 years, 95% CI = 2.1–2.4 years) at the time of the first assessment.

When owners reported both coughing and nasal discharge at the first assessment, the respective horses developed RAO significantly more often (6 of 14 horses with occasional coughing and nasal discharge combined, 43%) than horses without reported respiratory signs (7%;  $P < .001$ , Table 2). The odds ratio was determined to be 9.9 (95% CI = 2.5–40.0). Sensitivity of nasal discharge and occasional coughing combined as a predictive sign for RAO was 55%, specificity was 89%. Time intervals did not differ between horses with occasional coughing and nasal discharge combined (mean = 2.3 years, 95% CI = 2.0–2.7 years) and healthy horses (mean = 2.3 years, 95% CI = 2.1–2.4 years) classified at the first assessment ( $P = .90$ ).

**Influence of Age, Sex, Coat Color, and Environmental Factors (Bedding, Time Spent Outdoors) on the Risk of Developing RAO.** None of these investigated factors showed significant effects on the development of RAO (Table 1). There were no differences regarding the time intervals for any of these factors (results not shown), except for the factor time outdoors. The difference in the time interval between the group 0–4 h time spent outdoors compared to >4 h of time spent outdoors was 3.3 months ( $P = .05$ ).

**Table 1.** Association of the development of RAO with signalment and environmental factors in the half-sibling families.

Variable	HOARSI Second Assessment			P-value
	1 or 2 (healthy/ IAD)	3 or 4 (RAO)	Total	
Age				
6–9 years	40 (89%)	5 (11%)	45 (100%)	$P = .89$
10–15 years	59 (88%)	8 (12%)	67 (100%)	
Total	99 (88%)	13 (12%)	112 (100%)	
Sex				
Stallions and geldings	47 (89%)	6 (11%)	53 (100%)	$P = .93$
Mares	52 (88%)	7 (12%)	59 (100%)	
Total	99 (88%)	13 (12%)	112 (100%)	
Coat color				
Brown	35 (87.5%)	5 (12.5%)	40 (100%)	$P = 1.0$
Other colors	33 (89%)	4 (11%)	37 (100%)	
Total	68 (88%)	9 (12%)	77 (100%)	
Bedding				
Straw	88 (89%)	11 (11%)	99 (100%)	$P = .65$
Without straw	11 (85%)	2 (15%)	13 (100%)	
Total	99 (88%)	13 (12%)	112 (100%)	
Time outdoors				
0–4 hours	75 (88%)	10 (12%)	85 (100%)	$P = .73$
4-multiple hours	23 (92%)	2 (8%)	25 (100%)	
Total	98 (89%)	12 (11%)	110 (100%)	

RAO, recurrent airway obstruction; IAD, inflammatory airway disease.

## Unrelated Population

**Effects of Occasional Coughing and Nasal Discharge on the Risk of Developing RAO.** Horses that showed occasional coughing at the time of the first assessment developed RAO more frequently than horses without any respiratory signs ( $P = .006$ , Table 2). Six (25%) of the 24 horses with occasional coughing at the first assessment developed RAO, whereas only 2 (3%) of the 60 previously healthy horses developed RAO. The odds ratio was 9.7 (95% CI = 1.8–52.1). Sensitivity of occasional coughing as a predictive sign for RAO was 75%, and specificity was 76%.

Time intervals of the 2 assessments were significantly different ( $P = .009$ ) between horses with occasional coughing (mean = 4.7 years, 95% CI = 4.6–4.7 years) and healthy horses (mean = 4.7 years, 95% CI = 4.7–4.8 years) at the time of the first assessment, but the difference of the mean time interval was small (0.8 months).

Nasal discharge in the first assessment was not associated with an increased likelihood of signs related to RAO in the second assessment. Two of 12 horses (17%) with nasal discharge developed RAO in the second assessment ( $P = .13$ ). The time intervals between the two assessments differed significantly between horses with nasal discharge (mean = 4.7 years, 95% CI = 4.6–4.7 years) and horses without respiratory clinical signs (mean = 4.7 years, 95% CI = 4.7–4.8 years;  $P = .003$ ) by 1.1 months.

The risk of developing RAO in horses with coughing and nasal discharge combined at the time of the first assessment did not differ compared to that in horses without respiratory clinical signs. Only 1 of 8 horses with occasional coughing and nasal discharge combined (13%) developed RAO in the second assessment ( $P = .32$ ). The intervals between the 2

**Table 2.** Association of the development of RAO with occasional coughing, nasal discharge, and occasional coughing and nasal discharge combined in the related half-sibling families and in the unrelated replication population, respective  $P$ -values, odds ratios, 95% lower and upper confidence limits, sensitivity, specificity, positive and negative predictive values.

	P-value	OR	
		(95% CI)	Sensitivity Specificity
Half-sibling families			
Mucous nasal discharge	<.001	7.0 (2.0–24.6)	62% 81%
Occasional coughing and mucous nasal discharge	<.001	9.9 (2.5–40.0)	55% 89%
Unrelated population			
Occasional coughing	.006	9.7 (1.8–52.1)	75% 76%

95% CI, 95% confidence interval; OR, odds ratio.

assessments did not differ ( $P = .13$ ) between horses without respiratory signs (mean = 4.7 years, 95% CI = 4.7–4.8 years) and horses with coughing and nasal discharge combined (mean = 4.7 years, 95% CI = 4.6–4.8 years) classified at the time of the first assessment.

**Influence of Age, Sex, Coat Color, and Environmental Factors (Bedding, Time Spent Outdoors) on the Risk of Developing RAO.** Age, sex, coat color, bedding, and time outdoors were not associated with risk of developing RAO (Table 3). There were no significant differences regarding the time intervals for any of these factors (results not shown), except for the factor time outdoors (mean difference between group 0–4 hours time spent outdoors and group >4 hours of time spent outdoors: 0.6 months,  $P = .02$ ).

### Discussion

This study shows that occasional coughing and mucous nasal discharge might be early indicators of an increased risk of developing RAO. It has been proposed that small airway disease (used as a synonym for IAD) is a precursor of chronic obstructive pulmonary disease (used as a synonym for RAO).<sup>2</sup> However, many owners are oblivious to the early signs of IAD, which might later progress to RAO with its potentially

debilitating consequences.<sup>2</sup> Still to date, the assumption that horses with IAD are at increased risk of developing RAO remains speculative and has not been appropriately investigated.<sup>3–5</sup> To our knowledge, the present results provide the first scientific basis for this assumption. Specifically, our data demonstrate the predictive value of horse-owner reported mild clinical signs when evaluating the risk to develop RAO.

In the half-sibling group, horses with nasal discharge alone had a 7-fold and those with nasal discharge and coughing combined an almost 10-fold increased risk of developing RAO. Specificities for these clinical signs were good, but sensitivities were low. Across all groups most horses did not develop RAO. Even with occasional coughing and nasal discharge combined, the majority remained free of RAO within the subsequent years.

In the unrelated horses, investigated as an independent replication population, horses with occasional coughing developed RAO more frequently compared to horses without respiratory signs. A considerable proportion (25%), but still a clear minority, of those with occasional coughing became RAO-affected within 4–5 years. Overall, specificities and sensitivities of occasional coughing for developing RAO in horses are comparable to the values of a recently developed composite asthma predictive score in children.<sup>22</sup>

A markedly lower proportion of unrelated horses without any clinical signs developed RAO (3% within 4.1–5 years) than the offspring of the RAO-affected stallions (7% within 1.3–3.8 years). This is likely because of genetic effects, the most important predisposing factor for the development of RAO besides hay feeding.<sup>8,9,11,25,26</sup> Family history of RAO is itself an important predictor for developing the disease with risks estimated at 3–5 fold when one of the parents is affected.<sup>11,26</sup> In human asthma, a recent study also found that family history is an independent predictor for children to develop persistent asthma within 4 years.<sup>22</sup> Genetic effects could also potentially explain why coughing was a strong predictor of risk for RAO in the unrelated group, while in the half-sibling group there was only a trend for cough to predict RAO. Alternatively, this could be a statistical power issue or because of the shorter time interval between first and second examinations in the half siblings compared to the replication group. The available data do not allow us to test these hypotheses, however. These questions would have to be investigated in further studies.

In both populations, the tested individual (signalment) and environmental factors had no influence on the development of RAO, which excluded important potential confounding effects. The most important of all environmental effects in the development of RAO, hay feeding<sup>10–13,27</sup> was deliberately eliminated by defining continuous hay feeding throughout the study period as an inclusion criterion for all horses. It was somewhat surprising, however, that age group had no effect, because age has previously been shown to be an independent risk factor for the development of RAO.<sup>11,26</sup> All horses in the present study were at least

**Table 3.** Association of the development of RAO with signalment and environmental factors in the unrelated replication population.

Variable	HOARSI Second Assessment		Total	P-value
	1 or 2 (healthy/ IAD)	3 or 4 (RAO)		
<b>Age</b>				
5–12 years	47 (92%)	4 (8%)	51 (100%)	$P = .48$
13–24 years	32 (86.5%)	5 (13.5%)	37 (100%)	
Total	79 (90%)	9 (10%)	88 (100%)	
<b>Sex</b>				
Stallions and geldings	37 (90%)	4 (10%)	41 (100%)	$P = 1.0$
Mares	42 (89%)	5 (11%)	47 (100%)	
Total	79 (90%)	9 (10%)	88 (100%)	
<b>Coat color</b>				
Brown	46 (87%)	7 (13%)	53 (100%)	$P = .31$
Other colors	33 (94%)	2 (6%)	35 (100%)	
Total	79 (90%)	9 (10%)	88 (100%)	
<b>Bedding</b>				
Straw	66 (88%)	9 (12%)	75 (100%)	$P = .35$
Without straw	13 (100%)	0 (0%)	13 (100%)	
Total	79 (90%)	9 (10%)	88 (100%)	
<b>Time outdoors</b>				
0–4 hours	34 (92%)	3 (8%)	37 (100%)	$P = .73$
4–multiple hours	45 (88%)	6 (12%)	51 (100%)	
Total	79 (90%)	9 (10%)	88 (100%)	

RAO, recurrent airway obstruction; IAD, inflammatory airway disease.



5 years old, and the results do not apply to younger animals.

Our data indicate that occasional coughing, which was a predictor of RAO in both populations, is an important indicator for an increased risk of developing RAO. In contrast, the association of nasal discharge with the development of RAO, which had a marked effect in the half-sibling group only, could not be reproduced in the unrelated population. Previous studies have shown that compared to coughing nasal discharge is a less sensitive indicator for pulmonary disease in general<sup>23</sup> and in particular for RAO.<sup>16,28,29</sup> Classification bias is expected to be low with the owner-reported clinical signs used. The HOARSI, which includes owner-reported frequency of coughing and presence of nasal discharge, has proven to have a high reliability of classification.<sup>8,16</sup> In addition, relevant confounding effects associated with the time intervals could be excluded in both populations. Nonetheless, data collection on only 2 occasions constitutes a weakness of the present study. Based on our present data, it is impossible to determine if the development of RAO was the result of a gradual worsening or if there was a more abrupt deterioration between the 2 assessments. In addition to more frequent assessments, future studies should also include clinical and ancillary examinations, particularly BALF cytology and pulmonary function testing, which would give a more precise and conclusive diagnosis of IAD<sup>1</sup> and RAO<sup>4</sup> than owner-based questionnaires alone. Cytologic characterization would also allow to investigate which forms of IAD, neutrophilic, eosinophilic or mast-cell type,<sup>1,30</sup> are precursors of RAO. The neutrophilic form seems most likely to be responsible, because its presence is most often accompanied by coughing.<sup>30</sup>

In conclusion, mild, but persistent respiratory signs, particularly occasional coughing, can indicate an increased risk of developing RAO. Thus, when a horse presents with signs persisting for more than 2 months, further clinical and ancillary examinations should be considered—especially when a familial history of RAO is known. This will help the owner and clinician to decide on the need for prophylactic measures such as environmental changes with the goal of avoiding the development of RAO.

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## Supporting Information

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

**Fig S1. (A-D) Half-sibling families:** Percentages (%) of horses without any clinical signs (A; 7%) or showing occasional coughing (B; 19%,  $p = .08$ ), nasal discharge (C; 35%,  $p < .001$ ; OR = 7.0, 95% CI = 2.0 – 24.6) or both (D; 43%,  $p < .001$ ; OR = 9.9, 95% CI = 2.5 – 40.0) in the first assessment, developing RAO or staying healthy in the second assessment (1.3–3.8 years later).

**Fig S2. (A-B) Unrelated replication population:** Percentages (%) of horses, which either developed RAO or stayed healthy in the second assessment (4.1–5 years later). Horses without clinical signs (A; 3%) in the first assessment developed RAO less frequently, compared to horses with occasional coughing (B; 25%) at the time of the first assessment ( $p = .006$ ; OR = 9.7, 95% CI = 1.8 – 52.1).