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ACVIM Consensus Statement

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Exercise Induced Pulmonary Hemorrhage in Horses: American College of Veterinary Internal Medicine Consensus Statement

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Background: Published studies of exercise-induced pulmonary hemorrhage (EIPH), when assessed individually, often provide equivocal or conflicting results. Systematic reviews aggregate evidence from individual studies to provide a global assessment of the quality of evidence and to inform recommendations.

Objectives: Evaluate evidence to determine: if EIPH adversely affects the health, welfare or both of horses; if EIPH affects the athletic capacity of horses; the efficacy of prophylactic interventions for EIPH; and if furosemide affects the athletic capacity of horses.

Animals: None.

Materials and Methods: *Systematic review*. A panel of 7 experts was formed to assess evidence in the peer reviewed literature addressing each of the 4 objectives. Methodology followed that of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE). Publications were assessed for quality of evidence by working groups of the panel, and a summary of findings was presented in tables. Recommendations were based on quality of evidence and were determined by a vote of the panel.

Results: Much of the evidence was of low to very low quality. Experimental studies frequently lacked adequate statistical power. There was moderate to high quality evidence that EIPH is progressive, is associated with lung lesions, that it adversely affects racing performance, that severe EIPH (Grade 4) is associated with a shorter career duration, that furosemide is efficacious in decreasing the incidence and severity of EIPH, and that administration of furosemide is associated with superior race performance.

Conclusions and clinical significance: Strong recommendation that EIPH be considered a disease and a weak recommendation for use of furosemide in management of racehorses with EIPH.

Key words: Bleeding; Lungs; Physiology; Respiratory.

Exercise-induced pulmonary hemorrhage (EIPH) is bleeding that occurs from the lungs of horses during exercise. It occurs in the majority of Thoroughbred and Standardbred racehorses and in many other horses subjected to strenuous exercise.

The perceived importance of EIPH and use of furosemide is illustrated by the results of an internet search[a] (May 26, 2014) that returned over 45,000 results on the term "bleeders in horses", 113,000 on "EIPH", 890,000 using "Lasix and horse", and 905,000 results for "furosemide and horse". Web of Science searches conducted on May 26, 2014 using the terms "exercise-induced pulmonary hemorrhage" or "exercise-induced pulmonary hemorrhage" AND "horse" yielded 368 results, "EIPH" AND "horse" 224 results, and "furosemide or frusemi-

Abbreviations:

ACVIM	American College of Veterinary Internal Medicine
EIPH	exercise induced pulmonary hemorrhage
EP	evidence profile
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
SoF	summary of findings

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de" AND "horse" 367 results. Further evidence of interest in these topics is the frequency of articles and opinion pieces in the nonscientific veterinary and lay literature.

For the purpose of this consensus statement, EIPH is defined as the presence of blood detected on tracheobronchoscopic examination after exercise, presence of red blood cells in bronchoalveolar lavage fluid, or both. There is no consensus about the concentration of red blood cells in bronchoalveolar lavage fluid that is diagnostic of EIPH, and the definition varies among reports. Interventions to prevent or decrease the severity of EIPH will be referred to as prophylaxis and not as "treatment" given that most interventions are applied before the horse exercises and that some clinicians consider treatment of EIPH to be the management of the consequences of EIPH after exercise.

This consensus statement addresses 4 topics related to EIPH and its prophylaxis in horses. It does not address regulatory issues such as detection of drug administration or the potential masking effect of furosemide on other medications or substances, the pathophysiology of EIPH, risk factors for the condition, or the effect of permitting use of furosemide on the health or racing career of horses.

The objective of this consensus statement is to review the evidence and provide findings and recommendations that address each of the following topics:

1 Does EIPH adversely affect the health, welfare or both of horses? This question is important because evidence of an adverse effect of EIPH on the health or well-being of horses has potential ramifications for use of horses for racing.
2 Does EIPH affect the athletic capacity of horses? An adverse effect of EIPH on athletic capacity might influence decisions on the use of interventions to decrease the severity or incidence of EIPH.
3 Are there effective prophylactic interventions for EIPH? The capacity to manage EIPH is dependent on the existence of medications or interventions that decrease the severity or incidence of EIPH.
4 Does furosemide affect the athletic capacity of horses? An association of furosemide administration with superior performance has been suspected since the drug was first used in race horses and continues to be contentious.[1]

We performed a systematic review providing a series of findings and recommendations rather than a narrative review because of the relatively large number of experimental and observational trials relevant to these topics and the importance of systematically ranking the quality of the evidence. Although both types of review have the capacity to provide a critical evaluation of the literature, only the systematic review is widely recognized as rigorous and, being based on clearly defined methodology, is less likely to be biased.

Increasingly, the shortcomings of providing only assessments of the quality of evidence as the outcome of a systematic review have been recognized, leading to the development of GRADE methodology (Grading of Recommendations Assessment, Development and Evaluation)] which provides a methodology for arriving at findings regarding the body of evidence and making recommendations based on these findings.[2,3] In addition to considering the strength of evidence, the GRADE process considers a number of other factors when making a recommendation (see Supplementary material).[4]

Because randomized controlled trials only rarely have been used in investigations related to EIPH, we expanded our consideration to studies of other designs. We also adopted the GRADE approach to evaluating the quality of evidence of individual studies and then developed a concise statement of our overall confidence in the results of all studies combined. Assessments of evidence included an assessment of the quality of the evidence and the direction of the effect.

Methods

The topic for this consensus statement was developed using policies and procedures of the American College of Veterinary Internal Medicine. The topic was selected after nomination from the ACVIM membership, and confirmed by the ACVIM Board of Regents. Nominations for membership of the consensus panel were solicited from leadership of the ACVIM and ECEIM, and composition and chair of the consensus panel were approved by the Board of Regents of the ACVIM. All members of the panel completed a conflict of interest declaration, which was provided to a representative of the Board of Regents of the ACVIM and the Chair of the panel. Potential conflicts of interest for each panel member are listed separately.

The consensus panel invited input to the process in an email to all members of the Large Animal Specialty and ECEIM on January 7, 2014. Three responses were received.

This consensus statement was developed by a systematic review of the scientific literature related to the 4 topics listed above. Consistent with the GRADE approach,[5] a series of subsidiary outcomes were defined for each of the 4 main topics and were defined as either "critical" or "important".[6] Critical outcomes were those clearly directly related to the topic (e.g. race performance as a critical subsidiary outcome for the topic of "association of EIPH with performance") whereas important outcomes were those related to mechanisms (e.g. blood gas tensions during strenuous exercise as an indirect estimate of the relationship of furosemide with performance, pulmonary fibrosis as an indicator of lung health) or indirect measures of a critical outcome (e.g. run time to fatigue on a treadmill, VO_{2max} as an indicator of athletic capacity). The scientific literature relevant to each of the subsidiary questions was then evaluated for relevance and strength of evidence and each study summarized in an "Evidence Profile" (EP) table.[5] Studies then were aggregated into a "Summary of Findings" (SoF) table that summarized the available literature.[7] Further details are available in the Supplementary material.

Exercise-induced pulmonary hemorrhage was defined as the presence of blood in the airways of horses after exercise. Blood could be detected by tracheobronchoscopic examination, or by enumeration of red blood cells or hemosiderophages in tracheal aspirates or bronchoalveolar lavage fluid. Exercise-induced pulmonary hemorrhage included both occult hemorrhage (evident only on tracheobronchoscopic or cytologic examination of the airways)

and epistaxis. Throughout this document EIPH refers to either outcome (occult EIPH or epistaxis). Epistaxis refers specifically to the presence of blood at the nostrils after racing.

Responsibility for developing the initial search and evaluation of the literature was delegated to a working group for each topic. Each working group then provided Evidence Profile tables, Summary of Findings tables and a written summary for evaluation by the whole panel. Discussion among working group members occurred by email and teleconference. See Supplementary material for details.

Results

Consensus was achieved on all findings by a unanimous vote.

Topic 1. What is the Impact of EIPH on Welfare and Health of Horses?

Exercise-induced pulmonary hemorrhage often is cited as an important factor adversely affecting the health and well-being of athletic horses without provision of evidence supporting the contention. Evidence of systematic examination of affected horses for clinical abnormalities such as fever, cough, or abnormal lung sounds is sparse (Table 1).

Critical Outcome. *Does EIPH produce clinical signs?*: The clinical signs of EIPH often are considered to include: blood in the airways detected by either tracheobronchoscopy or examination of tracheal aspirates or bronchoalveolar lavage fluid, poor performance, epistaxis, abnormalities detected on ultrasonographic or radiographic examination of the thorax, coughing, increased respiratory rate, respiratory distress or changes in behavior. The diagnostic accuracy of these signs varies or has not been well-evaluated. Presence of blood in the airways of a horse after exercise is considered the gold standard for diagnosis of EIPH. Tracheobronchoscopic detection and grading of blood in the trachea or bronchi has been validated as a means of assessing the severity of EIPH (but not the severity of the underlying lesions) and has clinical utility in that it is associated with measures of performance.[8,9] Athletic performance is likely a useful guide to the horse's health.

There is very low quality evidence that EIPH is not associated with coughing and coughing does not appear to be a reliable sign of the presence of EIPH detected by presence of hemosiderophages in tracheal lavage fluid.[10] We located no reports of the frequency of coughing in horses with EIPH diagnosed by tracheobronchoscopy.

Epistaxis after exercise generally is considered an indication of EIPH although epistaxis can result from other causes (e.g. trauma to the head or upper airways, ethmoidal hematoma, guttural pouch mycosis). In the 3 reports of examination of horses with EIPH as evidenced by epistaxis, no evidence of causes other than pulmonary hemorrhage as the source of the blood was identified. There is moderate quality evidence that epistaxis during or soon after exercise is attributable to EIPH.

Radiographic examination of the thorax of horses can demonstrate the presence of densities in the caudodorsal lung fields of some horses with EIPH. Many horses with EIPH have minimal to undetectable radiographic abnormalities and horses without a history of EIPH can have marked abnormalities. There is moderate quality evidence that radiographic examination has low sensitivity in detecting horses with EIPH.[11–14] There is very low quality evidence that ultrasonographic examination has high sensitivity (86%) and low specificity (26%) for detection of EIPH.[15] We identified no evidence regarding increased respiratory rate, respiratory distress, or changes in behavior as clinical signs of EIPH in horses after exercise.

Finding: *There is very low quality evidence of consistent clinical abnormalities in horses with EIPH, with the exception of presence of epistaxis after exercise for which there is moderate quality evidence.*

Important Outcome. *Does EIPH affect blood-gas exchange?*: Arterial blood gas tensions and blood (or plasma) lactate concentrations theoretically could be affected by EIPH. Four observational treadmill studies provided very low quality evidence that EIPH impaired arterial blood gas tensions during intense exercise.[16–19] Studies were marked by inconsistency and imprecision and serious risk of bias.

Three prospective observational studies provide only very low quality evidence that EIPH is associated with higher blood lactate concentrations during exercise.[16,18,19] Studies were marked by low numbers of horses, bias and inconsistency.

Finding: *There is very low quality evidence of an adverse effect of EIPH on arterial oxygen tension during exercise. There is very low quality evidence of an association between higher blood lactate concentrations and EIPH during strenuous exercise.*

Critical Outcome. *Is EIPH a cause of sudden death?*: Quality of evidence regarding the occurrence of sudden death was assessed subjectively because the published data were not appropriate for an EP or SoF. There is low quality evidence of an association between EIPH and sudden death of Thoroughbred horses during racing. Exercise-induced pulmonary hemorrhage occurs in the majority of horses during racing whereas sudden death occurs in 0.08 to 0.29 horses per 1,000 starts.[20] Pulmonary hemorrhage was considered to have contributed to the sudden death during or shortly after racing or training of 50 of 143 horses for which there was confirmation of the cause of death.[21] Other reports of association of pulmonary hemorrhage and death during racing are based on small numbers of cases. Although pulmonary hemorrhage can be present in horses that die suddenly, it is unclear if pulmonary hemorrhage is the primary cause of death or is secondary to another cause of death (e.g. acute heart failure resulting in sudden death and pulmonary hemorrhage). The risk of sudden death in horses with EIPH has not been determined in that an association between EIPH and subsequent sudden death during racing is unclear.

Finding: *There is low quality evidence that EIPH is causally associated with sudden death in race horses and we could locate no evidence of increased risk of sudden death in horses with EIPH.*

Table 1. Summary of Findings table for association of EIPH with health and welfare of horses.

	Quality assessment					Number of horses		Treatment effect			
Outcomes	Study design (n)*,†	Bias (n)	Inconsistency	Indirectness	Imprecision	Control	EIPH	Absolute	Relative	Strength of evidence	Comments
Does EIPH cause epistaxis?											
Presence of epistaxis after exercise	III (3)	None	None	Not serious (I)	None	1605 total examinations	736 EIPH cases identified	NA	Incidence of epistaxis in EIPH positive horses 0–6.2%	Moderate	EIPH is associated with epistaxis. Frequency of other causes of epistaxis after exercise is unclear but appears to be low
Does EIPH cause changes that can be detected using imaging techniques?											
Presence of lesions on plain radiographs	III (4)	Serious (3)	Serious (1)	Serious (4)	Serious (1)	10	51	Majority report increased density in caudodorsal lung fields	NA	low	No direct comparison possible among the 4 studies. No demonstration of utility of examination
Presence of changes detectable using ultrasonography	III (1)	Serious	NA	None	None	127	30	Diagnostic sensitivity of ultrasound 85.8% specificity = 25.7%.	NA	Low	Single study
Does EIPH cause coughing?											
Evidence of EIPH as a cause of coughing horses	III (1)	None	NA	Serious (indirect assessment of EIPH)	Serious – wide confidence intervals	148	100 coughing horses	OR 0.05–3.5	NA	Very low	No demonstration of coughing in horses with EIPH
Does EIPH affect blood gas exchange and blood lactate concentrations?											
Blood gas tensions during intense exercise	III (3)	Serious – no power estimate or confidence intervals around effect	Serious	None	Serious	22	126	NA	NA	Very low	No pooled estimates of effect available. Inconsistent results. Imprecise results
Blood lactate concentration during intense exercise	III (3)	Serious – no power estimate or confidence intervals around effect	Serious	None	Serious	34	38	NA	NA	Very low	No pooled estimates of effect available. Inconsistent results. Imprecise results
Does EIPH shorten the career of horses?											
Number of lifetime starts	III (1)	No	NA	No	No	744	Grade 4 horses had 15.2 fewer starts than Grade 0 horses	NA	Moderate	$P < .001$. No association between EIPH Grade and duration of career in months.	

Table 1. (Continued)

Outcomes	Quality assessment					Number of horses		Treatment effect		Strength of evidence	Comments
	Study design (n)*,†	Bias (n)	Inconsistency	Indirectness	Imprecision	Control	EIPH	Absolute	Relative		
Is EIPH associated with inflammation of the lung?											
Does EIPH cause inflammation in the lungs?	II (4) III (4)	Not serious	None	Serious (4)	Not serious	29	66	Evidence of low-grade inflammation only in horses instilled with autologous blood. No active inflammation in EIPH-affected animals	NA	Moderate	The 4 studies that used inoculation of autologous blood might not reflect processes occurring in EIPH
Does EIPH cause structural changes in the lung?											
Does EIPH cause structural changes in lungs.	III (7) IV (1)	Not serious	None	Not serious	Not serious	10	101	All studies hemosiderin, fibrosis and vascular remodeling in caudodorsal lung fields, 3 showed venous remodeling and 2 changes in bronchioles	NA	High	
Is EIPH a progressive condition?											
Is increasing age associated with greater risk or prevalence of EIPH?	III (4)	Serious – no power estimate or confidence intervals around effect	Serious	Serious -	Serious	569	788	Majority do not detect age effect, including after correction for number of starts.	NA	Very low	No pooled estimates of effect available. Inconsistent results. Imprecise results
Is increasing age associated with greater risk of epistaxis	III (1), IV (2)	Serious – no power estimate or confidence intervals around effect	Serious – explained by confounding of number of starts.	None	Not serious	1,253,150 race starts	NA	Increased risk of episataxis with increasing time spent racing or age.	NA	Low	No pooled estimates of effect available. Inconsistent results. Imprecise results
Is increasing volume of racing (starts, racing years) associated with increased risk of EIPH or epistaxis	III (2)	Not serious	Not serious	None	Serious	27347	588	OR Epistaxis ~2.8× for horses 2, 3, 4+ years versus 1 year racing OR for EIPH of 1.8 for ≥ 50 starts versus < 40 starts	1.2–5.3 1.1–2.8	Moderate	Thoroughbreds. Evidence of increase in OR with increasing racing volume
Does EIPH contribute to the pathogenesis of other diseases?											
No relevant publications identified											
Is epistaxis heritable?											
Calculated heritability of epistaxis	IV (2)	Moderate risk (2)	No	No	No	170,234 pedigrees analysed		Lifetime epistaxis risk $h^2 = 0.23–0.27$	NA	Low	Reporting of results in available studies impairs evaluation of the studies

†n = number of studies included.

*Study design (see Supplementary item 5) : Type I - Randomized, placebo controlled, blinded field or clinical trials (high quality RCTs) conducted under conditions of racing or competing. Initial level of evidence - High. Type II - Randomized controlled intervention trials (low quality RCTs) including treadmill studies. Initial level of evidence - Moderate. Type III - Non-randomized controlled trials and prospective observational studies. Initial level of evidence - Low. Type IV - Case series and retrospective observational studies. Initial level of evidence - Very low.

Critical Outcome. *Does EIPH shorten the career of horses?*: The association of EIPH with duration or quality of racing career can be assessed using either EIPH grading or epistaxis as a marker of EIPH severity. The 1 study addressing the association of severity of EIPH and duration of racing career used a single endoscopic examination and provided moderate quality evidence that EIPH Grade 4 is associated with a shortened racing career of Thoroughbred race horses in Australia.[22] Epistaxis is associated with retirement of horses from racing in Australia but whether this is attributable to biologic (i.e., disease) factors or is a consequence of the management of affected horses is unclear.[23] There is moderate quality evidence that EIPH of Grades 1–3 is not associated with a shortened racing career.[22]

Finding: *There is moderate quality evidence that EIPH Grade 1-3 is not associated with a shorter racing career of Thoroughbred horses. There is moderate quality evidence that Thoroughbred horses with epistaxis or Grade 4 EIPH have shorter careers.*

Important Outcome. *Is EIPH associated with inflammation in the lung?*: Early descriptions of airway inflammation (bronchiolitis) in EIPH lungs[24] are not supported by more recent investigations.[35] Experimentally, a single infusion of autologous blood into the airways is followed by increased numbers of alveolar macrophages and hemosiderophages and disappearance of blood with no residual inflammation at 14 days.[25–26] Blood instilled repeatedly also is cleared rapidly and does not result in lesions characteristic of EIPH.[27,28]

The evidence supporting airway inflammation as a cause of EIPH is very weak. During intense exercise, horses are more likely to bleed into regions of lung with local experimentally induced airway inflammation but the role this inflammation plays in the naturally occurring syndrome is unknown.[29] In a large investigation of Thoroughbred racehorses examined monthly, airway inflammation was associated with EIPH as defined both by visible bleeding and hemosiderophages in tracheal wash fluid but the relationship of these observations to recent exercise or racing was not considered.[30] Other large field investigations found no associations between EIPH score and airway inflammation,[31] between cough (a sign of airway inflammation) and number of hemosiderophages,[10] or between tracheal mucus score (a sign of lower airway inflammation) and EIPH score.[31]

Finding: *There is low quality evidence that EIPH leads to inflammation in either the pulmonary parenchyma or airways. There is very low quality evidence that inflammation causes EIPH.*

Critical Outcome. *Does EIPH cause lesions in the lungs?*: Worldwide, lesions are present in the lungs of EIPH-affected horses retired from racing because of repeated exercise-associated epistaxis or EIPH.[33,35,65,97] Similar but less severe lesions described in young horses in training need confirmation.[32] Both gross and microscopic EIPH lesions are bilateral and most prevalent in the caudodorsal region of the lung. Lesions extend to varying degrees along the dorsal border, but never occur in the cranioventral regions. Gross lesions include discoloration of the pleural surface with underlying firm parenchyma that does not fully deflate in excised lungs. Pleural discoloration is a consequence of hemosiderin accumulation that is accompanied by pleural and septal fibrosis and angiogenesis.[24,35] Vascular lesions include extensive remodeling of small pulmonary veins (100–200 μm outer diameter) characterized mainly by accumulation of adventitial collagen and, in some vessels, smooth muscle hyperplasia.[35] In the most severely affected vessels, the vascular lumen is markedly decreased. The distribution of venous remodeling, hemosiderin, and fibrosis is similar to the distribution of pulmonary blood flow in the equine lung.[33] Electron microscopy of lungs from recently exercised horses shows breaks in the capillary endothelium and basement membrane, interstitial and intra-alveolar accumulations of erythrocytes, and interstitial edema that are compatible with capillary stress failure consequent to high intravascular pressure.[34]

Finding: *There is high quality evidence that some horses with EIPH have extensive and characteristic pulmonary lesions.*

Critical Outcome. *Is EIPH a progressive condition?*: There are no studies that report on the incidence of EIPH in a group of horses followed over the course of their career. There is low quality evidence that EIPH detected by endoscopic examination is associated with age when confounding factors, including the number of starts, are not accounted for in the statistical analysis.[9,36,37,46] However, when the number of starts is included, age is not a risk factor for EIPH.[38]

Similarly, there is moderate quality evidence that age is a risk factor for epistaxis when confounding factors are not taken into account.[39–41] When career duration was included in analyses, years spent racing was a significant risk factor (although with considerable imprecision), whereas age was not.

Finding: *There is moderate quality evidence that EIPH is progressive and related to load of racing.*

Critical Outcome. *Does EIPH contribute to the pathogenesis of other diseases?*: We could identify no reports of studies investigating the relationship between EIPH and subsequent infectious or noninfectious lung disease.

Finding: *We did not locate evidence that EIPH is associated with development of other lung diseases.*

Critical Outcome. *Is EIPH heritable?*: Because EIPH of some form occurs in almost all racehorses, there is no phenotypic variance at the level of present/not present, rendering the question of heritability of EIPH likely irrelevant. There is low quality evidence that epistaxis is a heritable trait in racing Thoroughbreds.[42,43] The quality of the evidence is considered to be very low because of difficulties with case identification, inability to exclude non-EIPH related epistaxis, inability to completely characterize pedigrees, and because the heritability measured might be for factors that facilitate the passage of blood from lungs to nostrils rather for those than influence the severity of EIPH.

Finding: *There is no published evidence regarding the heritability of EIPH. There is very low quality evidence of an association of pedigree with occurrence of epistaxis.*

Topic 2. Does EIPH Affect Performance?

The high incidence of EIPH has prompted speculation that EIPH is an important cause of impaired performance in Thoroughbred racehorses. Although this belief is strongly held by many horsemen and veterinarians involved in the care of racehorses, others have suggested that EIPH might be associated with superior performance, being reflective of greater racing effort. Evaluating the association of EIPH with performance requires establishing outcomes or measurements of performance during racing or on the treadmill (Table 2).

Critical Outcome. *Is EIPH associated with the finishing position in a race?*: Seven studies reported on the association of EIPH with finishing position in the race (1 with moderate level of evidence and 6 with low and very low level of evidence). Two studies determined that EIPH detected by tracheobronchoscopic examination was associated with the likelihood of having inferior finishing position races.[44,45] One study examined 744 Thoroughbreds racing in Australia where race-day use of furosemide and nasal strips are prohibited.[45] The other examined 1,003 individual Thoroughbred racehorses (2,118 tracheobronchoscopic examinations) that all received furosemide and had been diagnosed previously with EIPH.[46] The study with the strongest evidence showed that horses that were EIPH negative or had EIPH grade 1 were more likely to win or finish in the first 3 positions.[45] In the 5 studies showing no effect of EIPH on finishing position, pre-race furosemide prophylaxis status for horses was unknown in 4 and unreported in the fifth.[9,37,47–49]

Finding: *There is moderate quality evidence that moderate to severe EIPH in Thoroughbred race horses is associated with increased likelihood of inferior finishing position in a race.*

Critical Outcome. *Is EIPH associated with the finishing time in a race?*: A single study examined 29 EIPH positive Standardbred horses that had at least 1 EIPH negative race.[48] Their average racing times were compared between EIPH positive and EIPH negative horses and no statistical significant difference was detected. The report was of very low quality because of apparent low statistical power, nonrandom selection of horses, and racing time was recorded only in winners.

Finding: *There is very low quality of evidence that EIPH in Standardbred racehorses is not associated with finishing time in a race.*

Critical Outcome. *Is EIPH associated with the distance a horse finishes behind the winning horse in a race?*: A single study evaluated the effects of EIPH on the distance a horse finishes behind the winning horse in a race.[45] Horses with EIPH severity Grade $\geq$1 finished significantly further behind the winner than did horses with no evidence of EIPH. For horses with EIPH distance finished behind the winner was associated with grade of EIPH with higher grades finishing further behind the winner. Post hoc testing indicated significant difference in distance finished behind the winner with horses with grade 2 EIPH compared with no evidence of EIPH.

Finding: *There is moderate quality evidence that Thoroughbred racehorses with more severe EIPH finish farther behind the winning horse in a race.*

Critical Outcome. *Is EIPH associated with race earnings?*: A single study evaluated the effects of EIPH on a horse's race earnings. Horses with EIPH severity grade $\leq$ 1 were about 3 times as likely to be in the highest decile for race earnings when compared to horses with EIPH severity Grade $\geq$2.[45]

Finding: *There is moderate evidence that severity of EIPH in Thoroughbred racehorses is negatively associated with a horse's race earnings.*

Critical Outcome. *Is there a dose response relationship between the severity of EIPH and performance?*: Three studies of horses racing on a racetrack reported evaluation of the effect of the severity of EIPH on performance.[45–47] The 2 studies providing moderate quality evidence indicated a negative association of the severity of EIPH and performance.[46,47] The strongest study found an apparent dose-response for distance finished behind the winning horse, but not for finishing position as measured categorically (i.e. winning or finishing in the top 3 positions).[45]

Finding: *There is low quality evidence of a dose-response relationship between severity of EIPH in Thoroughbred racehorses and severity of impaired performance.*

Topic 3. Are There Effective Prophylactic Interventions for EIPH?

All investigations of the effect of drugs and nonpharmacological management of EIPH have focused on prevention (i.e. prophylaxis). There are no reports of the efficacy of treatments to decrease severity or progression of lung lesions of EIPH-affected horses nor are there reports of treatment of horses with EIPH (i.e. management of the short term clinical consequences of an episode of EIPH). Likewise, there are no reports of efficacy of interventions applied during training to prevent EIPH during racing.

Critical Outcome. *Is furosemide effective prophylaxis for EIPH?*: A number of low quality investigations conducted both on the treadmill and on the racetrack judged furosemide ineffective as a treatment for EIPH (Table 3).[50–52] These studies simply judged the presence or absence of visible hemorrhage postexercise by endoscopy with no attempt to judge the severity of bleeding. Low quality studies demonstrated a decrease in the number of red blood cells in bronchoalveolar lavage fluid in horses performing standardized exercise tests on a treadmill.[53,54]There was a decrease in severity of EIPH identified in 2 high quality investigations that endoscopically graded bleeding in large numbers of horses running on the racetrack.[55,56]

Finding: *There is high quality evidence that furosemide (0.5–1 mg/kg administered IV 4 hours before strenuous exercise) decreases the severity and incidence of EIPH.*

Important Outcome. *Does furosemide affect pulmonary vascular pressure?*: Pertinent to EIPH, several moderate

Table 2. Summary of findings – Does EIPH affect performance?

	Quality Assessment						Summary of findings				
Outcomes	Study Design	Bias (n)	Limitations	Inconsistency	Indirectness	Imprecision	Summary of results	Results: YES/NO	Dose response (graded EIPH)	Strength of Evidence High, moderate, low, very low	Comments
Finishing position – Normal racing conditions	III (7)	Low risk (1) Moderate to High risk (6)	Very different approaches to data analysis. Most did not control for potential confounding	Inconsistencies in reported outcomes (performance) and methods of analysis	Nil	Minimal to moderate for pairwise comparisons in the high quality study. Serious for lower quality studies	High quality study for EIPH ≤1: OR for winning = 4.0 (1.5–14.3). OR for finishing in top 3 = 1.8 (1.1–3.1). No difference found in lower quality studies	2 studies found effects (1 high quality, 1 low quality)	Not detected	Mod (n = 1) Very low (n = 6)	Low power and confounding bias could have profound affected low-quality study
Finishing time – Normal racing conditions	III (1)	High risk	Low power, no control of potential confounding	N/A	Nil	Serious	n = 49 horses: EIPH Mean = 2:04.1 (SD = 2.1 second), Non-EIPH Mean = 2:03.3 (SD = 2.1 seconds)	n.s.	Not evaluated	Very low	Very low power
Distance finished behind winning – normal racing conditions	III (1)	Low risk	Low numbers of severely affected horses	N/A	Nil	Moderate for pairwise comparisons related to severe EIPH	n = 744 horses: EIPH ≥ 1 mean = 4.4 m (SE 1.2 m); EIPH Grade 0 mean = 2.6 m (SE 1.1 m)	Significant difference	Yes	Mod	Low numbers of severely affected horses
Race earnings (90th percentile or greater)	III (1)	Low risk	Low numbers of severely affected horses	N/A	Nil	Moderate for pairwise comparisons related to severe EIPH	n = 744 horses: OR for EIPH ≤1 = 3.0 (1.3–8.0) compared to EIPH ≥ 2	Significant difference	Not reported	Mod	Low numbers of severely affected horses
Dose Response Relationship between EIPH and Performance – Normal Racing Conditions	III (3)	Low risk (1) Moderate to High risk (2)	Very different approaches to data analysis. Most did not control for potential confounding. Low numbers of severely affected horses	Inconsistencies in reported outcomes (performance) and methods of analysis	Nil	Minimal to moderate for pairwise comparisons in the high quality study. Serious for lower quality studies.	Dose response relationship was identified in the high quality study for distance finished behind the winner, and was not identified for finishing position. Lower quality studies did not identify an effect.	1 study found an effect in 1 outcome.		Mod (n = 1) Very low (n = 2)	Confounding bias could have profoundly affected low-quality studies

Table 3. Summary of findings of efficacy of furosemide and other interventions for prophylaxis of EIPH.

	Quality Assessment					Number of horses		Treatment effect			
Outcomes	Study design (n)	Bias (n)	Inconsistency	Indirectness	Imprecision	Control	FUR	Absolute	Relative	Strength of evidence	Comments
Is furosemide is an effective prophylactic treatment for EIPH?											
EIPH quantified by scoring tracheal blood postexercise	I (2)	Low	No	No	No	211	211	65% of horses have decreased EIPH score when racing after furosemide	Horses are more likely to bleed after saline than after furosemide treatment	High	"High" evidence rating results from large n, randomized crossover trials, racing conditions, and scoring of tracheal blood
EIPH quantified by BALF RBC count after exercise	Type II (3)	Moderate	No	No	No	23	23	Furosemide reduced BAL RBC count.		Low	The correlation between BALF RBC count and EIPH score is unknown.
EIPH quantified by blood in trachea post exercise (Yes/No)	II (4) IV (1)	High	No	No	No	19 61	19 24	No effect of furosemide	NA	Very Low	None of these studies graded the severity of bleeding
Does furosemide affect pulmonary capillary blood pressure?											
Direct measurement of pulmonary vascular pressures	II (4)	Low	No	No	No	30	30	Furosemide (1 mg/kg, IV) reduced Pcap to 79% of control		Moderate	In treadmill studies, furosemide consistently reduces pulmonary capillary pressure in exercising horses

Table 3. (Continued)

Outcomes	Quality Assessment					Number of horses		Treatment effect		Strength of evidence	Comments
	Study design (n)	Bias (n)	Inconsistency	Indirectness	Imprecision	Control	FUR	Absolute	Relative		
Are nasal strips an effective prophylaxis for EIPH?											
EIPH quantified by blood in trachea post exercise (Yes/No)	II (1)	High	NA	No	Serious – Amount of blood not quantified	7	7	No effect of nasal strips		Low	Single study
EIPH quantified by BALF RBC count after exercise	II (3) III (1)	Low	No	No	No	24	43	Nasal strips reduced BAL RBC count.		Low	Small sample size and low power

quality treadmill investigations have consistently demonstrated that furosemide decreases pulmonary arterial and pulmonary wedge (left atrial) pressures and hence (calculated) pulmonary capillary and transmural pressure during intense exercise.[50,51,57–64] Such decreases in pressure might decrease the likelihood of capillary stress failure.[34]

Finding: *There is moderate quality evidence that furosemide reduces pulmonary vascular pressure during strenuous exercise.*

Critical Outcome. *Is aminocaproic acid an effective prophylaxis for EIPH?*: Two randomized, placebo-controlled treadmill studies found that aminocaproic acid (2–7 g, IV) given 2–4 hours before strenuous exercise test to fatigue did not decrease BALF red blood cells compared to saline placebo.[66,67] However, both studies provided very low quality evidence because of outcome measure imprecision and indirectness (risk of bias), and small sample size (6–8 horses).

Finding: *There is very low quality evidence that aminocaproic acid affects EIPH severity.*

Critical Outcome. *Are bronchodilators effective prophylaxis for EIPH?*: Clenbuterol administered IV alone or in combination with furosemide (10 minutes before exercise) does not affect pulmonary hemodynamics,[50,68] but drug effect on EIPH severity was not assessed. Nine days of clenbuterol treatment in resting horses after intrabronchial instillation of autologous blood did not result in significant change in numbers of red blood cells or hemosiderophages in BALF compared to control.[69] Another study with few horses showed no effect of atropine on EIPH and inconclusive results with ipratropium nebulization.[70] All studies provided very low to low quality evidence because of the low number of horses and lack of blinding.

Finding: *There is very low quality evidence that bronchodilators affect EIPH.*

Critical Outcome. *Are corticosteroids effective prophylaxis for EIPH?*: One treadmill study reported that 3 days of dexamethasone did not prevent EIPH but EIPH severity was not assessed.[71] Neither 9–10 days of inhaled beclomethasone nor oral prednisolone treatment changed either red blood cell number or hemosiderophages in BALF of resting horses after intrabronchial instillation of autologous blood.[69]

Finding: *There is very low quality evidence that corticosteroids affect EIPH severity.*

Critical Outcome. *Are nonsteroidal anti-inflammatory drugs effective prophylaxis for EIPH?*: Very low quality treadmill studies failed to detect an effect of either phenylbutazone (with furosemide) or flunixin meglumine on EIPH (evaluated as presence or absence of blood on endoscopic examination).[61,72]

Finding: *There is very low quality evidence that nonsteroidal anti-inflammatory drug treatment affect EIPH.*

Critical Outcome. *Is pentoxifylline an effective prophylaxis for EIPH?*: Two treadmill studies found that pentoxifylline had no effect on pulmonary hemodynamics when used alone or in combination with furosemide. An effect of pentoxifylline on EIPH (evaluated as pres-

ence or absence of blood on endoscopic examination) was not detected although EIPH severity was not assessed.[58,73]

Finding: *There is very low quality evidence that pentoxifylline affects EIPH.*

Critical Outcome. *Are there other medications that are effective for prophylaxis of EIPH?*: Carbazochrome (with furosemide),[74] equine serum concentrate,[75] conjugated estrogens,[67] endothelin 1-A antagonist[76], nedocromil,[77] nitric oxide,[78] and sildenafil[79] have been investigated as prophylaxis of EIPH in single studies for each drug. The studies are all of very low quality because they were conducted on a treadmill, used low numbers of horses, and the severity of EIPH was not assessed.

Although reportedly used in practice, we could locate no scientific evidence of the efficacy of aspirin or ethamsylate.

Finding: *The studies provided very low quality evidence that these drugs affect EIPH severity.*

Critical Outcome. *Do nasal strips prevent EIPH?*: A low quality treadmill investigation assessing presence or absence of postexercise blood in the airways stated nasal strips were ineffective in preventing EIPH, however, the severity of bleeding was not graded.[80] 4 other studies, undertaken in a limited number of horses, showed that horses had a significant decrease in postexercise BALF RBCs when exercised with nasal strips.[53,54,81,82]

Finding: *There is low quality evidence that nasal strips decrease severity of EIPH.*

Important Outcome. *Are there other miscellaneous nonpharmacological treatments to prevent EIPH?*: Neither herbal formulations[83] nor inhaled water vapor[84] showed evidence of efficacy in preventing EIPH. The studies were of very low quality.

Rest and water restriction before strenuous exercise have been recommended, however there is no scientific evidence that those practices decrease the incidence or severity of EIPH. Nonetheless, several racing jurisdictions have ruled to enforce rest periods ranging from 2 to 3 months for horses with epistaxis.

Finding: *The studies provided very low quality evidence that herbal preparations or inhaled water vapor affect EIPH severity.*

Topic 4. Does Furosemide Affect Performance?

A variety of outcome measures have been used in an attempt to assess performance in horses racing on a track (Table 4). However, standardization of measurements is difficult because numerous intrinsic factors (e.g., sex, age, horse quality, fitness level) and extrinsic factors (e.g., jockey, distance, track conditions, environmental conditions) vary among races and can create confounding bias in results. Control of extrinsic and intrinsic factors is more feasible when horses model race experiences by running on high-speed treadmill, but this model inherently limits the generalizability of results. Additionally, most treadmill studies suffer from small sample size and consequently have low statistical power. The ability to extrapolate performance data obtained during treadmill studies to actual performance during racing has not been established.

Most studies conducted on racetracks have used adjusted race time to cover a standardized distance as an outcome measure of performance[85–90] whereas others have used finish position,[85,89] racing speed or earnings.[85] Treadmill studies have evaluated performance as distance covered or time that horses run until the onset of fatigue.[74,91–93] Alternatively, or in addition, some treadmill studies have reported the effect of furosemide on the energetic cost of locomotion.[91,94,95]

Critical Outcome. *Does furosemide affect performance of horses running on a racetrack?*: Studies in Thoroughbred and Standardbred racehorses have been performed under natural racing conditions[85,88–90] and under simulated racing conditions on a track.[86,87] The study with the highest sample size (n = 22,589) found that mean estimated mile-equivalent race times were 0.56 to 1.09 second faster for horses receiving furosemide prophylaxis compared to horses not receiving furosemide[85] All 4 studies conducted during normal racing conditions were rated as providing moderate quality of evidence because design and analyses helped to minimize risk of bias, used relevant outcome measures (e.g., racing time adjusted for distance), were adequately powered, and showed consistent results. Two studies performed under simulated race conditions did not detect an effect of furosemide on performance as compared to placebo.[86,87] However, both studies provided very low quality evidence because of outcome measure imprecision (risk of bias), small sample size (6–10 horses), and slow running speed achieved during race simulation.

Studies that investigated other performance measures, such as finish position, average racing speed, and race earnings also identifed a consistent benefit for horses receiving furosemide before racing compared to untreated horses.[85,89] The largest study evaluated sex differences, and found that the benefits of furosemide administration on performance were more marked in males and in horses $\leq$6 years old.[85] These studies were considered to have moderate quality of evidence for these outcomes. No studies investigated the mechanism for superior performance.

Finding: *There is moderate quality evidence that furosemide administered IV 4 hours prior to racing is associated with improved racing outcomes in Thoroughbred and Standardbred racehorses.*

Important Outcome. *Does furosemide affect performance of horses running on a treadmill?*: Five studies examined the effect of furosemide administered to horses performing a standardized test on a high-speed treadmill. Two studies found statistically longer time to fatigue in horses treated with furosemide.[92,93] Furosemide administration before a treadmill test improved the energetic cost of locomotion in 3 studies.[91,94,95]

Quality of evidence for all of these studies was rated down because relevance of performance on a treadmill compared to that on a racetrack is not known, considering that the effect of jockey or sulky and of other horses in the race cannot be replicated in the laboratory (indirectness). Also, performance on treadmill is typically

Table 4. Summary of findings concerning the effect of furosemide on performance.

	Quality Assessment					Number of horses		Treatment effect			
Outcomes	Study design (n)	Bias (n)	Inconsistency	Indirectness	Imprecision	Control	FUR	Absolute	Relative	Strength of evidence	Comments
Performance on the racetrack – Normal racing conditions	III (4)	Low risk (4)	No	No	No	6,001	17,260	−0.12 to −1.09 s*	−0.68 to −0.88%	High	Time to cover a given distance in furosemide treated horses relative to controls.
Performance on the racetrack – Simulated racing conditions	I (1) II (1)	Moderate risk (2)	No	Serious	Very serious	16	16	n.s.		Very low	One study recorded racing time with a stopwatch and in the other, horses raced maximally only during last ¼ mile. Small sample size and very low power
Finish position in race	III (2)	Low risk (1) Moderate risk (1)	No	No	No	5,854	16,804	OR win = 1.4 −1.5	N/A −26%	High	Odds of winning or Improvement in finishing position with furosemide
Treadmill performance	I (5)	Low risk (1) Moderate risk (4)	No	No	No	33	33	13.9 s	N/A	Moderate	Performance measured as extra time run before fatigue with furosemide

n.s., not statistically significant. *$P < 0.05$

judged based on the onset of fatigue which is a subjective assessment that can be influenced by lack of treatment concealment (imprecision).

Finding: *There is low quality evidence that furosemide administered IV 4 hours before treadmill exercise results in delayed onset of fatigue and improved energetic cost of locomotion.*

Discussion and Recommendations

The consensus panel found that there is good quality evidence that the presence of pulmonary lesions in racehorses is associated with epistaxis or repeated diagnosis of EIPH and low quality evidence of no effect of EIPH, excluding epistaxis, on well-being or health of horses. The presence of lesions in lungs of horses with EIPH substantiates our strong recommendation that EIPH be considered a disease and not a variably manifested normal result of strenuous activity in horses. There is only low quality evidence that the disease is progressive but the evidence allows the panel to make a weak recommendation that EIPH be considered a progressive disease, recognizing that further research is needed.

The panel found that there is high quality evidence that furosemide is effective in the prophylaxis of EIPH and makes a weak recommendation for its use in management of racehorses with this disease. The recommendation is weak because the panel recognizes that conditions for use of furosemide in some horses, such as racehorses, is regulated by racing jurisdictions that must consider a broad range of factors (not just efficacy) and that there continues to be extensive discussion among these stakeholders regarding policies and perceived need for furosemide prophylaxis.[96]

The panel makes no recommendation regarding other pharmacological interventions for the prophylaxis of EIPH because of the absence of studies or the very low to low quality of evidence.

The panel notes that many studies intended to test the efficacy of an intervention for prophylaxis of EIPH do not include adequate reporting of the details of the study to permit full evaluation of the quality of evidence, were likely to have a high frequency of Type 2 error rates because of small sample sizes, were conducted on a treadmill (with unknown relevance to actual competition), and did not assess dose–response relationships. Of particular concern to the panel was the large number of reports that had negative results (i.e., the study did not detect an effect of the intervention) but did not make an *a priori* attempt to establish adequate study size or to consider statistical power in interpretation of their results. Failure to detect an effect of the intervention in a study with inadequate statistical power is not the same as demonstration of no effect.

The panel found that there is moderate quality evidence that moderate to severe EIPH is associated with decreased athletic capacity by Thoroughbred racehorses.

The panel found that there is high quality evidence that furosemide administration is associated with improved performance by Thoroughbred and Standardbred racehorses.

Footnote

[a] www.google.com

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Supporting Information

Additional Supporting Information can be found online in Supporting Information: