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


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 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
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. In addition to considering the strength of evidence, the GRADE process considers a number of other factors when making a recommendation (see Supplementary material).

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, a series of subsidiary outcomes were defined for each of the 4 main topics and were defined as either “critical” or “important”. 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$_{2\max}$ 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. Studies then were aggregated into a “Summary of Findings” (SoF) table that summarized the available literature. Further details are available in the Supplementary material.
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 caudo-dorsal 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 imprecision.

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.

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

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Study design</th>
<th>Bias (n)</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Control</th>
<th>EIPH</th>
<th>Absolute</th>
<th>Relative</th>
<th>Strength of evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does EIPH cause inflammation in the lungs?</td>
<td>II (4)</td>
<td>Not serious</td>
<td>None</td>
<td>Serious (4)</td>
<td>Not serious</td>
<td>29</td>
<td>66</td>
<td></td>
<td></td>
<td>NA</td>
<td>Moderate</td>
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<td>EIPH - Evidence of low-grade inflammation only in horses instilled with autologous blood. No active inflammation in EIPH-affected animals.</td>
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<tr>
<td>Does EIPH cause structural changes in the lung?</td>
<td>III (7)</td>
<td>Not serious</td>
<td>None</td>
<td>Not serious</td>
<td>Not serious</td>
<td>10</td>
<td>101</td>
<td></td>
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<td>NA</td>
<td>High</td>
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<tr>
<td>All studies hemosiderin, fibrosis and vascular remodeling in caudodorsal lung fields, 3 showed venous remodeling and 2 changes in bronchioles.</td>
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<tr>
<td>Is increasing age associated with greater risk or prevalence of EIPH?</td>
<td>II (4)</td>
<td>Serious - no power estimate or confidence intervals around effect</td>
<td>Serious</td>
<td>Serious</td>
<td>Serious</td>
<td>569</td>
<td>788</td>
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<td>NA</td>
<td>Very low</td>
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<td>Majority do not detect age effect, including after correction for number of starts.</td>
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<tr>
<td>Is increasing age associated with greater risk of epistaxis</td>
<td>III (4), IV (2)</td>
<td>Serious - no power estimate or confidence intervals around effect</td>
<td>Serious</td>
<td>Serious - explained by confounding of number of starts.</td>
<td>Not serious</td>
<td>1,253.50</td>
<td>NA</td>
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<td>NA</td>
<td>Low</td>
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<tr>
<td>Increased risk of epistaxis with increasing time spent racing or age.</td>
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<tr>
<td>Is increasing volume of racing (starts, racing years) associated with increased risk of EIPH or epistaxis</td>
<td>II (2)</td>
<td>Not serious</td>
<td>None</td>
<td>Not serious</td>
<td>Serious</td>
<td>27347</td>
<td>588</td>
<td></td>
<td></td>
<td>NA</td>
<td>Moderate</td>
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<tr>
<td>OR Epistaxis ~2.8x for horses 2, 3, 4+ years versus 1 year racing. OR for EIPH of 1.8 for ≥ 50 starts versus &lt; 40 starts.</td>
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<td>Does EIPH contribute to the pathogenesis of other diseases?</td>
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<td>NA</td>
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<td>No relevant publications identified.</td>
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<tr>
<td>Is epistaxis heritable?</td>
<td>IV (2)</td>
<td>Moderate risk (2)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>170,234 pedigrees analysed</td>
<td>Lifetime epistaxis risk h² = 0.12–0.27</td>
<td>NA</td>
<td>Low</td>
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<td>Reporting of results in available studies impairs evaluation of the studies</td>
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<td>h = number of studies included.</td>
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<tr>
<td>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.</td>
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</table>
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 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 racehorses. There is low quality evidence that EIPH Grade 1–3 is not associated with a shortened racing career.

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 EIPH have shorter careers.

Important Outcome. Is EIPH associated with inflammation in the lung? Early descriptions of airway inflammation (bronchiolitis) in EIPH lungs are not supported by more recent investigations. 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. Blood instilled repeatedly also is cleared rapidly and does not result in lesions characteristic of EIPH.

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 inflammation of a naturally occurring syndrome is unknown. 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 with epistaxis or racing was not considered. Other large field investigations found no associations between EIPH score and airway inflammation, between cough (a sign of airway inflammation) and number of hemosiderophages, or between tracheal mucus score (a sign of lower airway inflammation) and EIPH score.

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

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. Similar but less severe lesions described in young horses in training need confirmation. 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. Vascular lesions include extensive remodeling of small pulmonary veins (100–200 \( \mu \)m outer diameter) characterized mainly by accumulation of adventitial collagen and, in some vessels, smooth muscle hyperplasia. 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. 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.

Similarly, there is moderate quality evidence that age is a risk factor for EIPH. 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 start, are not accounted for. EIPH duration measured might be for factors that facilitate the passage of blood from lungs to nostrils rather than influence the severity of EIPH.

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. The quality of the evidence is considered to be very low because of difficulties with case identification, inability to exclude non-EIPH related epistaxis, and the 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 than those that 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.

Finding 1: There is moderate quality evidence that EIPH in Standardbred horses is associated with decreased likelihood of inferior finishing position in a race.

Finding 1: There is moderate quality evidence that EIPH in Thoroughbred racehorses is associated with increased likelihood of inferior finishing position in a race.

Critical Outcome. Is EIPH associated with finishing time in a race?: A single study examined 29 EIPH horses (2,118 tracheobronchoscopic examinations) that all received furosemide and nasal strips are prohibited. The other examined 1,003 individual Thoroughbred racehorses that all received furosemide and had been diagnosed previously with EIPH.

Finding: There is moderate quality evidence that furosemide prophylaxis is associated with decreased 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.

Finding: There is moderate quality evidence that an EIPH horse finishes farther behind the winning horse than did horses with no evidence of EIPH.

Finding: There is moderatle quality evidence that EIPH in 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 ≤ 1 were about 3 times as likely to be in the highest decile for race earnings when compared to horses with EIPH severity Grade ≥ 2.

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

Finding: There is moderate quality evidence that the severity of EIPH during racing is negatively associated with a horse’s race earnings.

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

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

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

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Study Design</th>
<th>Bias (n)</th>
<th>Limitations</th>
<th>Inconsistency in reported outcomes (performance) and methods of analysis</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Summary of results</th>
<th>Results: Dose response (graded EIPH)</th>
<th>Strength of Evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finishing position - Normal racing conditions</td>
<td>III (7)</td>
<td>Low risk (1)</td>
<td>Moderate to High risk (6)</td>
<td>Very different approaches to data analysis. Most did not control for potential confounding</td>
<td>Nil</td>
<td>Mild to moderate</td>
<td>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.</td>
<td>2 studies found effects (1 high quality, 1 low quality)</td>
<td>High, moderate, low, very low</td>
<td>Low power and confounding bias could have profoundly affected low-quality study</td>
</tr>
<tr>
<td>Finishing time - Normal racing conditions</td>
<td>III (1)</td>
<td>High risk</td>
<td></td>
<td>N/A</td>
<td>Nil</td>
<td>Serious</td>
<td>High quality study for EIPH Mean = 2.041 (SD = 2.1 seconds), Non-EIPH Mean = 2.033 (SD = 2.1 seconds)</td>
<td>n.s.</td>
<td>Very low</td>
<td>Very low power</td>
</tr>
<tr>
<td>Distance finished behind winning - normal racing conditions</td>
<td>III (1)</td>
<td>Low risk</td>
<td></td>
<td>N/A</td>
<td>Nil</td>
<td>Moderate for pairwise comparisons related to severe EIPH</td>
<td>Significant difference</td>
<td>Yes</td>
<td>Mod</td>
<td>Low numbers of severely affected horses</td>
</tr>
<tr>
<td>Race earnings (90th percentile or greater)</td>
<td>III (1)</td>
<td>Low risk</td>
<td></td>
<td>N/A</td>
<td>Nil</td>
<td>Moderate for pairwise comparisons related to severe EIPH</td>
<td>Significant difference</td>
<td>Not reported</td>
<td>Mod</td>
<td>Low numbers of severely affected horses</td>
</tr>
<tr>
<td>Dose Response Relationship between EIPH and Performance – Normal Racing Conditions</td>
<td>III (3)</td>
<td>Low risk (1)</td>
<td>Moderate to High risk (2)</td>
<td>Very different approaches to data analysis. Most did not control for potential confounding. Low numbers of severely affected horses</td>
<td>Nil</td>
<td>Minimal to moderate for pairwise comparisons in the high quality study. Serious for lower quality studies.</td>
<td>1 study found an effect in 1 outcome.</td>
<td>Mod (n = 1)</td>
<td>Very low</td>
<td>Confounding bias could have profoundly affected low-quality studies</td>
</tr>
</tbody>
</table>

Summary of results

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Bias (n)</th>
<th>Limitations</th>
<th>Inconsistency in reported outcomes (performance) and methods of analysis</th>
<th>Indirectness</th>
<th>Imprecision</th>
</tr>
</thead>
<tbody>
<tr>
<td>III (7)</td>
<td>Low risk (1)</td>
<td>Moderate to High risk (6)</td>
<td>Very different approaches to data analysis. Most did not control for potential confounding</td>
<td>Nil</td>
<td>Minimal to moderate</td>
</tr>
<tr>
<td>III (1)</td>
<td>High risk</td>
<td></td>
<td>N/A</td>
<td>Nil</td>
<td>Serious</td>
</tr>
<tr>
<td>III (1)</td>
<td>Low risk</td>
<td></td>
<td>N/A</td>
<td>Nil</td>
<td>Moderate for pairwise comparisons related to severe EIPH</td>
</tr>
<tr>
<td>III (1)</td>
<td>Low risk</td>
<td></td>
<td>N/A</td>
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</tr>
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<td>III (3)</td>
<td>Low risk (1)</td>
<td>Moderate to High risk (2)</td>
<td>Very different approaches to data analysis. Most did not control for potential confounding. Low numbers of severely affected horses</td>
<td>Nil</td>
<td>Minimal to moderate</td>
</tr>
</tbody>
</table>

Notes:
- n.s. = Not significant
- OR = Odds Ratio
- SD = Standard Deviation
- SE = Standard Error
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Quality Assessment</th>
<th>Number of horses</th>
<th>Treatment effect</th>
<th>Strength of evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is furosemide an effective prophylactic treatment for EIPH?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EIPH quantified by scoring tracheal blood postexercise</td>
<td>I (2)</td>
<td>Low</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>EIPH quantified by BALF RBC count after exercise</td>
<td>Type II (3)</td>
<td>Moderate</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>EIPH quantified by blood in trachea post exercise (Yes/No)</td>
<td>II (4) IV (1)</td>
<td>High</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Does furosemide affect pulmonary capillary blood pressure?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct measurement of pulmonary vascular pressures</td>
<td>I (4)</td>
<td>Low</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
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.\textsuperscript{50,51,57–64} Such decreases in pressure might decrease the likelihood of capillary stress failure.\textsuperscript{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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{69} Another study with few horses showed no effect of atropine on EIPH and inconclusive results with ipratropium nebulization.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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),64 equine serum concentrate,75 conjugated estrogens,67 endothelin 1-A antagonist76, nedocromil,77 nitric oxide,78 and sildenafil79 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 ethanolamine.80 While nasal strips were ineffective in preventing EIPH, absence of postexercise blood in the airways stated by authors 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:** 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 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 formulations83 nor inhaled water vapor84 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 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 ≤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 finish position, average racing speed, and race earnings also identified consistent benefits 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 ≤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.
Table 4. Summary of findings concerning the effect of furosemide on performance.

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

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.

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**

Funded by ACVIM.

**Conflict of Interest Declaration:** Couetil: None disclosed. Hinchecliffe: Travel and accommodation costs only paid to workshop in January 2013 hosted by California Thoroughbred Owners. No consulting or other contracts related to this consensus statement. No current research funding. Previous receipt of funds for EIPH research from the Grayson Jockey Club Research Foundation and the Rural Industries Research Corporation (Australia). Knight: Official Veterinarian Racing New South Wales, Australia; Official Veterinarian, Australian Turf Club. Morley: Dr. Morley has been compensated for speaking on topics related to EIPH in conferences and meetings conducted by the ACVIM, the American Association of Equine Practitioners, the Horseman’s Benevolent Protection Association, California Thoroughbred Owners, and the Jockey Club. He has received funding for research related to EIPH from the Grayson-Jockey Club Research Foundation and the Racing Medication and Testing Consortium, and support-in-kind for research from the Daily Racing Form. He has no other interests in assets, products, or services related to this consensus statement, financial, or otherwise. Robinson: Travel and accommodation costs paid to speak at “International Summit on Race Day Medication: EIPH and the Racehorse (Belmont September 2011) and at workshop in January 2013 hosted by California Thoroughbred Owners. He has been a coinvestigator on an EIPH-related grant from Grayson Jockey Club Foundation. Sweeney: Pennsylvania State Horse Racing Commission (Chair 2008-2013, Member 2013 – present). van Erck: None disclosed.

**Off-label Antimicrobial Declaration:** Authors declare no off-label use of antimicrobials.

**References**


46. Costa MFM, Thomassian A. Evaluation of race distance, track surface and season of the year on exercise-induced pulmonary...


Supporting Information

Additional Supporting Information can be found online in Supporting Information: