Where Do We Go From Here?
Exercise Induced Pulmonary Hemorrhage (EIPH) & Race-day Medication (a scientist’s perspective)

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This Presentation – Opinions of a Scientist:

- Background
- Review some of our research
- What are the lessons learned?
- Opinions on future direction
Exercise-Induced Pulmonary Hemorrhage

- Hemorrhage into the terminal airways caused by rupture of the tissue barrier between blood vessels and airways.

- Very prevalent with high intensity exercise
  - Only the most severe cases demonstrate epistaxis
    - 0.25% to 1.0% of starts
  - Less severe bleeding occurs in at least 75% of racehorses (perhaps all)
  - Acute deaths may be a different disease

- Epistaxis described for centuries
  - e.g. Bartlet’s (Bleeding) Childers
    - Grandsire of Eclipse
Tracheobronchoscopic Assessment of EIPH in Horses

- **Grade 0** = No blood detected.
- **Grade 1** = One or more flecks of blood, or \( \leq 2 \) short, narrow (<10% of tracheal surface) streams.
- **Grade 2** = One long stream of blood (>half the length of the trachea) or >2 short streams occupying <\( \frac{1}{3} \) of the tracheal circumference.
- **Grade 3** = Multiple, distinct streams of blood covering >\( \frac{1}{3} \) of the tracheal circumference, with no blood pooling at thoracic inlet.
- **Grade 4** = Multiple, coalescing streams of blood covering more than 90% of the tracheal surface, with blood pooling at the thoracic inlet.
Prevalence and Severity of EIPH

744 Horses racing in Victoria, Australia
(Hinchcliff, Morley, et al., JAVMA 2005; 227:768-774)

≥Grade 2 in 18.0%

167 Horses racing at the Vaal, South Africa
(Hinchcliff, Morley, Guthrie, JAVMA 2009; 235:76-82)

≥Grade 2
• Placebo 24%
• Lasix 8%

2,118 Horses racing in Rio de Janeiro, Brazil
(Costa and Thomassian, EVJ 2006; S36:487-489)

≥Grade 2 in 35%

1,005 Horses racing in South Africa
(Saulez [thesis] 2007)

≥Grade 2 in 24%
Why Do Racehorses Have EIPH??

What causes this tissue barrier to rupture?

- Horses experience tremendous increases in blood pressure during exercise.
- 3× to 4× greater increases in pulmonary BP compared to other species.
- Also, negative pressure is created in airways during inspiration.
- Difference between positive BP and negative airway pressure creates tremendous “shear forces” across delicate terminal airways.
Furosemide (Lasix) & EIPH

- Most common prophylaxis
- First used for EIPH in 1960’s
  - Probably intended as hypotensive therapy
  - Analogy of epistaxis associated with severe hypertension in humans.

Efficacy of furosemide for EIPH:

- For 40 years treatment has largely been based on anecdotal testimony from trainers and veterinarians.
- Prior to 2009:
  - No evidence that treatment prevented EIPH
  - Inconclusive evidence about decreasing EIPH severity
    (Sweeney et al 1984; Pascoe et al 1985; Sweeney et al 1990; Erickson et al 1990; Manohar et al 1997, etc)
Furosemide effects

- Potent yet very safe diuretic
  - Decreased body weight (2-4% or ~20-50 lbs, dose dependant)
  - Increased PCV, TP
  - Decreases pulmonary artery pressure up to 20%
  - Transient hypochloremia, hypokalemia, hypocalcemia
    - Does not cause osteoporosis!
  - Mild alkalosis (not magnitude of $\text{H}_2\text{CO}_3$ dosing)
- Bronchodilatory effect (blocks bronchoconstriction)
Variable Race-Day Lasix Dosing of TB Racehorses at PHA (‘94-’98) n= 10,323
Race-Day Furosemide Medication

Very controversial

- Potential influence on athletic performance
  - Public interest, betting, tax revenues
- Animal wellbeing

$35M to $100M annually in U.S. for race-day furosemide administration (TB, QH, and STB)

- ~400,000 doses/year in U.S.
- Image of the veterinary profession
  - Financial benefit to veterinary profession
- Image of Trainers/Owners
Racing + Lasix = Controversy
(Controversy = Important Question)

Industry Questions when we started our research:

- Lasix and cheating (masking agent)
- Lasix and Performance?

- **40 years** without conclusive evidence of efficacy!
  - Small, inconclusive studies, mostly treadmill
  - Why argue about allowing use when we don’t know if it works?

- Everyone has mostly assumed that EIPH harms horses
  - Performance?
  - Wellbeing?
Race-Day Furosemide Treatment

Very Common in North America!

1997-1998
- About 75% of all TB starts
- About 23% of all STB starts

By about 2005
- >90% of TB starts
- >50% of STB starts

Especially Common in High-Profile Races
- All 132 North America-based starters in the 2008 Breeders Cup races.
- All qualified starters in the 2009 Kentucky Derby.

Why Did Use Become More Common?
Effect of furosemide on performance of Thoroughbreds racing in the United States and Canada

Diane K. Gross, Paul S. Morley, Kenneth W. Hinchcliff, Thomas E. Wittum

Objective—To determine the effect of furosemide use on performance of Thoroughbreds and Standardbreds (STBs) faces at tracks in the United States and Canada during 1997.

Design—Cross-sectional study.

Animals—All Thoroughbreds and STBs that had raced in 1997 in jurisdictions that had records of furosemide use.

Procedure—Race records were analyzed by the use of regression weighted ANOVA procedures to determine differences in estimated 6-furlong sprinting speed, race earnings, and component analyses of the severity of bleeding.

Furosemide is commonly used in Thoroughbreds and Standardbreds, and there is evidence that it may result in increased performance. However, the effect of furosemide on performance in standardbreds has not been evaluated. The present study was designed to examine the effect and the performance-enhancing effect of furosemide on Thoroughbreds and Canada;

22,589 TB Horses Racing in 1997

- Horses Receiving Furosemide
  - Ran Faster
  - More likely to win
  - More likely to earn money

- Similar findings in STBs
Decreased severity of EIPH
(Sweeney et al 1984; Pascoe et al 1985; Sweeney et al 1990; Erickson et al 1990; Manohar et al 1997; Hinchcliff et al 2009)

Decreased body weight (energy expenditure)
(Hinchcliff et al., 1993; Hinchcliff et al., 1996; Zawadzkas et al., 2006)

Increase VO$_2$ max ~ 5% (weight)
(Bayly et al., 1999; Zawadzkas et al., 2006)

Induction of metabolic alkalosis
(Harkins et al., 1993, Hinchcliff et al., 1998)

Bronchiolar relaxation - reversal of bronchoconstriction
(Broadstone et al., 1991)
Strong Associations!

Unlikely countered by any unmeasured bias
- However, were better horses more likely to receive Lasix in 1999?

What causes improved performance
- EIPH prevention/amelioration?
- Other effects (e.g., weight loss)?
- Mixture?
A panel [from the] AAEP is reporting to members that a recent study linking the use of Lasix to faster racing times is flawed by weak analysis and the prejudices of the authors.
One Year Later – AAEP 2000:
... after citing our work and calling it some of the strongest conducted to date:

“I think we need to accept that horses receiving furosemide will run faster than if they don’t receive furosemide.”

Warwick Bayly
744 horses racing in Australia in 2004

- CONCLUSIONS: Horses with EIPH (≥ Grade 2):
  - Less likely to win.
  - Had slower race times.
  - Earned less money.
  - Finished greater distance behind winner.
Efficacy of furosemide for prevention of exercise-induced pulmonary hemorrhage in Thoroughbred racehorses

Kenneth W. Hinchcliff, BVSc, PhD, DACVIM; Paul S. Morley, DVM, PhD, DACVIM; Alan J. Guthrie, BVSc, PhD

Objective—To evaluate the efficacy of furosemide for prevention of exercise-induced pulmonary hemorrhage (EIPH) in Thoroughbred racehorses under typical racing conditions.

Design—Randomized, placebo-controlled, blinded, crossover field trial.

Animals—167 Thoroughbred racehorses.

Procedures—Horses were allocated to race fields of 9 to 16 horses each and raced twice, 1 week apart, with each of the 2 races consisting of the same race field and distance. Each horse received furosemide before the other, with the order of administration being randomized. Each horse was assigned to one of two treatment protocols. Horses were scored on a scale from 0 to 5 with a value of 0 assigned to normal values. Results were analyzed by means of various statistical methods.

Results—Horses were submitted to exercise-induced pulmonary hemorrhage (EIPH) at a ratio of 3.3 to 4.4 (EIPH). Furosemide treatment did not significantly affect the EIPH scores.

Conclusions and Clinical Relevance—Furosemide decreased the incidence of EIPH in the typical conditions in South Africa.
Is Furosemide Effective For Preventing or Limiting EIPH??

Goals for Study Design

- The industry needed and deserved a clear, unequivocal answer
- Highest quality results: state-of-the-art design
- Applicable to conditions of actual use in the field
- Adequate study power
Experimental Design

Randomized, cross-over, triple blinded, placebo-controlled field trial

- Random allocation to treatment order
- Cross-over design to ensure maximum statistical power
- Placebo-controlled to ensure treatment effect is attributable to drug
- Blinding of all involved (participants, field investigators, data analysts) until analysis of data completed for primary outcomes to prevent observer bias
- Field trial to maximize ability to extrapolate results to other racehorses
Experimental Design

- Horses were recruited to race using typical methods (nominated by trainers for specific race conditions).
  - 12 Races (max 16 runners)
  - 1000, 1300, and 1600 meter races (approximately 5, 6.5, and 8 furlongs)

- Horses assigned fields by professional handicapper using methods standard to the industry.

- Two races, 1 week apart
  - Half of each field received furosemide or placebo prior to the first race.
  - Alternative treatment was given prior to second race.
  - Same conditions for the two races (field, post position, equipment, jockey, time of day, etc.)
Treatments

- **Furosemide (Salix)**
  - 500 mg IV (10 ml)
  - Why this dose?
  - Maximum allowable in most jurisdictions
  - We were not sure there was ANY effect

- **Saline (10 ml)**
  - Colored with vitamin B complex (0.1 ml per liter)

- Visually identical
Among 120 horses experiencing any EIPH when treated with placebo, 81 (67%) had reduction of ≥ 1 grade when treated with furosemide.
Results:

Effect of furosemide

Best Summary of Effect, controlling for age and effects of repeated observations:

- **EIPH ≥ 1** (any EIPH)
  The odds of EIPH were **3.3 to 4.4 times greater** in horses receiving placebo compared to horses treated with furosemide.

- **EIPH ≥ 2** (moderate to severe EIPH)
  The odds of EIPH were **6.9 to 11.0 times greater** in horses receiving placebo compared to horses treated with furosemide.
Why didn’t we look at performance in the SAFE Study??

- Primary Reason: This study was not designed to look at race performance as an outcome.
- There were simply not enough horses to look at race times!
Research Challenges

Small differences in performance are important, but it requires more study ‘power’ to identify small average differences.

<table>
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<th>Number of Subjects Needed</th>
<th>Average Difference in Race Time Between Performances (sec)</th>
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<tr>
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Conclusion

Prerace administration of furosemide (500 mg IV) markedly decreased both the incidence and severity of EIPH in Thoroughbred race horses racing in South Africa.
Now What?

Our Quote: "... The challenge will now be for countries such as Australia, England, Hong Kong and South Africa that do not currently permit race-day use of furosemide, to balance the animal-welfare aspect of being able to prevent or reduce the condition against the imperatives for drug-free racing. Additionally, instituting race-day administration of furosemide would be a significant added expense to racing."
Is this an Objective Response?

Or is (another) action that does not fully consider the real questions about the issue??
What We Know Today

- It is clear that EIPH is a common disorder of exercising horses that impairs racing performance.
- The frequency and severity of EIPH is reduced by medication with furosemide (at least at maximal doses).
- However furosemide is also associated with superior performance.

Given this knowledge of EIPH, there logically follow a number of other questions that must be addressed in order to develop a logical, objective policy on EIPH in racehorses.
Morley, Hinchcliff & Guthrie: Questions that need to be addressed

- **Does EIPH adversely affect the long term health and well being of race horses?**
  - We know of no studies that critically address this important question.
  - Are strict rules regarding ‘bleeders’ warranted?
  - If EIPH adversely affects the health of horses, development and use of methods to prevent EIPH would be indicated.

- **Is there evidence of a familial predisposition to EIPH?**
  - Current knowledge is minimal, and only addresses epistaxis
  - If there is a familial pattern, what is the genetic basis?

- **Are there treatments, other than furosemide, that are effective in preventing or meliorating EIPH without an effect on performance?**
  - **IF** EIPH adversely affects the health and wellbeing of horses, then critical evaluation of prophylactic or therapeutic interventions is absolutely necessary.
  - Let us not repeat previous mistakes past!
Racehorses, Attendance, Betting (and politics?)

Figure 29: Leading horseracing nations – betting, horses and attendances

Bubble size represents aggregate attendance
Conclusions:

These critical unknowns must be addressed before sound policies on management of EIPH *that place the wellbeing of the horse as the first priority* can be developed and implemented.
Questions?
Today: Countries That Officially Permit Race-Day Administration of Furosemide**

- Argentina
- Brazil
- Canada
- Chile
- Peru
- Saudi Arabia
- United States
- Venezuela

**Used during training
In many countries

Source: International Federation of Horseracing Authorities
Does EIPH Affect Wellbeing?

What would you think?
Does EIPH Affect Health?

- Of course it does... doesn’t it??
- Evidence of bleeding in lungs of aged racehorses (O'Callaghan et al.)
- Experimental challenge (Bayly et al.)
  - 25, 50, 100 ml blood in one lung
    - No effect on exercise
  - 100 ml blood bilaterally
    - Bld gas, O₂ Sats, Max O₂ Consumption
- Inject blood into parenchyma
- Repeated bleeding? (Derksen et al., Pasco et al.)
  - Repeated infusion into airways
  - Bronchiolitis?
Typical EIPH Regulations

- Vary by jurisdiction, regulated by the local racing authority.
- Epistaxis during racing or timed works leads to imposed lay-off.
  - 1 mo, 2-3 mo, 3-6 mo, lifetime ban
  - North America → **WITHIN 365 DAYS**
  - Europe, Asia, Australia, South Africa → **LIFETIME**
- Justified?
  - Does resting horses after bleeding actually help?
  - Does frequency of bleeding affect the severity of impact?
Good studies generally raise more questions than they answer!

As told to me by Dr. Hugh Townsend in 1990
EIPH Scores in Horses Receiving Both Treatments

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Among 120 horses experiencing any EIPH when treated with placebo, 81 (67%) had reduction of ≥ 1 grade when treated with furosemide.
Older Studies: Furosemide and Performance

Sweeney et al., 1990
- **COMPLEX** design
- Used handicapping methods for comparison of horses in different races
- Evaluated adjusted 1 mile equivalent racing times for up to 3 races

Effects of furosemide on the racing times of Thoroughbreds

Corinne Raphel Sweeney, DVM; Lawrence R. Soma, VMD; Abby D. Maxson, VMD; Joseph E. Thompson, BA; Susan J. Holcombe, BS; Pamela A. Spencer, ScM

Race 1

665

336 EIPH + 51%

329 EIPH -

Race 2

FUROSEMIDE

62 EIPH + 26%

173 EIPH -

Race 3

60 EIPH + 43%

79 EIPH -

Total EIPH + 51% 70% 85%

Data from Sweeney et al 1990
Effects of furosemide on the racing times of Thoroughbreds

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Older Studies: Furosemide and Performance

No association detected

Observational Studies

- Tobin et al., 1978; Milne et al., 1980
  - 6 Standardbreds
  - 8 furlong time trials
  - Trend toward decreased racing times when horses received furosemide
  - Difference not statistically detectable

- Tobin et al., 1978
  - Race records for 58 Standardbreds
  - Compared race times at 8 furlongs before and after EIPH diagnosis
  - Furosemide treated horses had increased race time of 0.14 sec, but no statistically detectable difference

- Soma et al., 1985
  - 128 horses at 4 tracks
  - Compared time/distance in 5 races before and 5 races after EIPH diagnosed
  - Trend toward enhanced performance with furosemide administration, no statistically detectable difference
  - Results inconsistent