Update on Equine Respiratory Disease

Mark Crisman, DVM, MS, DACVIM
Pfizer Animal Health
Virginia–Maryland Regional College of Veterinary Medicine

Agenda

- Equine herpesvirus–1 & (EHV–4)
  - Overview of current outbreak in cutting horses
  - EHV facts
  - EHV protection
- Equine Influenza (EIV facts and protection)
- Respiratory disease (bacterial)
- Therapeutic intervention (update on antibiotics)
- Questions

How common is acute infectious upper respiratory disease in horses?

A National Estimate of Acute Infectious Upper Respiratory Disease (IURD) and Risk Factors Associated with Infection for Horses in the United States During 1998–1999
Diane K. Gross, DVM; Paul S. Morley, DVM, PhD, Diplomate ACVIM; et al.
AAEP Proceedings, vol 46, 2000
How common is acute infectious upper respiratory disease in horses?

- To determine the rate of undifferentiated IURD (+ strangles) in horses in the US
- NAHMS– 1034 operations with 3+ resident horses (racetracks not included)
- Signs; cough, nasal discharge, fever, depression, anorexia…
- Results; 1.5 ± 0.2 horses developed IURD out of every 100 horses.
- Relied on owners/trainers to report occurrence

Surveillance programme for important equine infectious respiratory pathogens in the USA


Downloaded from veterinaryrecord.bmj.com on June 29, 2011

US Equine Respiratory Pathogens

- 24 month study
- 761 samples submitted
  - fever, coughing or nasal discharge
- 201 / 761 (26.4%)
  - PCR positive for one or more pathogens
    - EHV–4 (82 cases)
    - EIV (60 cases)
    - S. equi (49 cases)
    - EHV–1 (23 cases)
Equine Herpes Virus

- Commonly affects younger horses – weaning to 2-3 years
- Spread via inhalation & direct contact (ubiquitous in equine populations)
- Natural immunity is short lived (60 days)
- EHV-1 & 4 primary concern to horses– latent in lymph nodes of respiratory tract (EHV1) and trigeminal nerve ganglia (EHV4)
- Once infected, they carry the virus for life
- EHV 2 & 5 new players?

Differences between EHV-1 & EHV-4

- EHV-1 and EHV-4 are 70% genetically similar
- EHV-1
  - Upper respiratory
  - Abortion
  - Newborn Still Birth
  - Neurological
  - Mainly D712 point mutated EHV-1 strain
- EHV-4
  - Mainly Upper Respiratory

EHV Risk factors

- Horses under stressful situations
- Horses in large groups
EHV: Recognizing the Signs

- Fever and/or cough
- Nasal discharge
- Mild Limb edema
- Poor appetite and depression
- Abortion
- Poor anal / tail tone
- Inability to retract penis
- Ataxia
- Bladder paresis
- Fecal incontinence
- Muscle fasciculation
- Increased respiratory rate
  - (>14 b/min)

Equine Herpes Virus (EHV)
- Utah outbreak summary

  - 421 primary exposures
    - 1685 secondary/tertiary exposures
  - 88 confirmed EHV-1 or EHM cases
    - 58 from primary exposures
    - 30 from secondary/tertiary exposures
  - 12 dead or euthanized
    - 10 from primary exposures
    - 2 from secondary exposures

EEE—though December 28, 2010

231 cases

- 1 – Maryland
- 1 – New Jersey
- 1 – Virginia
- 10 – New York
- 4 – Massachusetts
- 1 – New Hampshire
- 57 – Michigan
- 4 – Ohio
- 8 – Alabama
- 20 – Mississippi
- 93 – Florida
- 24 – GA, IL, IN, TX, WI

http://diseasemaps.usgs.gov/eee_us_veterinary.html
EHV: To test or not to test.....

- Normally would reserve testing for individuals showing clinical signs
  - Non-clinical horses have been documented to shed EHV-1 via respiratory secretions
- However, there is benefit to testing clinically normal individuals if there has been EHV exposure
  - If individual has 2 consecutive negative tests, 7–10 days apart, the horse can be considered free of disease

Submit Blood and Nasal Swab–PCR

Viral presence (blood vs. nasal swab) will vary depending on stage of disease

- Early in disease
  - Nasal swab (+)
  - Blood (–)
- Mid-disease
  - Nasal swab (+)
  - Blood (+)
- Late in disease
  - Nasal swab (+/–)
  - Blood (+)

Viral presence (blood vs. nasal swab) will vary depending on stage of disease

- Early in disease
  - Nasal swab (+)
  - Blood (–)
- Mid-disease
  - Nasal swab (+)
  - Blood (+)
- Late in disease
  - Nasal swab (+/–)
  - Blood (+)
Submit Blood and Nasal Swab—PCR

Viral presence (blood vs. nasal swab) will vary depending on stage of disease

- Early in disease
  - Nasal swab (+)
  - Blood (−)
- Mid-disease
  - Nasal swab (+)
  - Blood (+)
- Late in disease
  - Nasal swab (+/−)
  - Blood (+)

Equine Herpesvirus

AAEP recommendations

- There is no vaccine labeled for the neurologic form of EHV-1
- Respiratory Disease EHV-1
  - Vaccination (dependent upon age and risk)
    - Annually
    - Every 6 months (most common)
    - Every 2–3 months (horses at high risk)
    - Bivalent vaccine (EHV-1&4) recommended **

EHV vaccines—antigen load

- Flu/Rhino combos
  - 30–33 Million Plaque Forming Units (PFU’s)
- Prodigy
  - 100 Million PFU’s
  - No challenge data with EHM
- Rhinomune
  - Modified Live
  - EHM challenge data available
- Pneumabort K
  - 133 Million PFU’s
  - EHM challenge data available
  - Contains Army 183 and Ab4 strains of EHV-1
    - Both are D752 genotype
Equine Herpesvirus

- There is no vaccine labeled for the neurologic form of EHV-1, but.....
  - Will help establish a level of protection via improved herd immunity
  - Vaccination can reduce the level of viral shedding during an outbreak
  - Stimulates mucosal antibodies
  - Very short-lived phase of immunity
  - Two vaccines have been shown to suppress viremia in experimental challenge with D752 strain

EHV Challenge Study

Colorado State University

- Evaluate immunity
  - challenge with Findlay 03, $5 \times 10^7$ pfu
  - Blinded, randomized challenge trial
  - 8 ponies in each group
  - Treatments:
    - Pneumabort K
    - Rhinomune
    - Placebo

<table>
<thead>
<tr>
<th>Months</th>
<th>V1</th>
<th>V2</th>
<th>V3</th>
<th>Ch</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Viremia post-challenge with Findley OH03

- Control
  - 6/8 viremic
  - 13 total viremic days
- Rhinomune
  - 4/8 viremic
  - 5 total viremic days
- Pneumabort K
  - 2/8 viremic
  - 3 total viremic days

Control of EHV-1 viremia and nasal shedding by commercial vaccines, Goehring, et al, Vaccine 28 (2010 5203-5211)
New EHV-1 study—Cornell

Wagner, B., Wimer, C., Freer, H., Osterrieder, N., Erb, H.N.

Infection of peripheral blood mononuclear cells with neuropathogenic equine herpesvirus type-1 strain Ab4 reveals intact interferon- induction and induces suppression of anti-inflammatory interleukin-10 responses in comparison to other viral strains

Veterinary Immunology and Immunopathology (2010), doi:10.1016/j.vetimm.2011.06.032

- RacL11 (respiratory strain)
- NY03 (abortogenic strain)
- Ab4 (neurotropic strain)

Equine Influenza

- Influenza virus
  - (A1 & A2)
- Highly contagious
  - Horses inhale virus
- Particularly prevalent in young horses
  - Generally seen in horses 2 years of age and older
- Major concern in areas of high horse population density
- Disease increases risk of secondary bacterial infection
Equine Influenza
• Infects & replicates in ciliated epithelial cells in upper & lower respiratory tract
• Results in de-ciliation of large areas w/in 4 to 6 days
• Incubation period= 1 to 3 days
• Fever, harsh dry cough= release of large amounts of virus
• Serous...mucopurulent nasal discharge, myalgia, inappetance, enlarged lnn.

Normal trachea
• Image courtesy of Dr. Issel and Gluck Center

Trachea after cilia destroyed by flu
• Image courtesy of Dr. Issel and Gluck Center
**Immunological Protection from EIV—Summary**

- Dependent on different immune mechanisms at both local and systemic level
- Systemically— IgGa and IgGb responses associated w/ protection and likely depends on an INFγ mediated Th1 immune response
- Mucosally— production of IgA critical and typically depends on Th2 immune response

**Vaccination**

- Primary goals; (1) to reduce clinical signs, (2) shorten convalescent period, (3) reduce shedding
- Ideally; provide long-term immunity, efficient memory response & cross protection
- Vaccine efficacy= clinical protection, absence of pyrexia, cough and discharge
- Virological protection= absence of virus in secretions
Relatedness of Equine Influenza Virus (EIV) A/Equine/Kentucky/97 with Recent Circulating EIV and Canine Influenza Virus (CIV) Based on Comparison of Hemagglutinin Gene Sequences

<table>
<thead>
<tr>
<th>Virus</th>
<th>% Homology</th>
</tr>
</thead>
<tbody>
<tr>
<td>EIV A/Equine/Kentucky/02</td>
<td>99.4</td>
</tr>
<tr>
<td>EIV A/Equine/Ohio/03</td>
<td>98.8</td>
</tr>
<tr>
<td>CIV A/Canine/Florida/03</td>
<td>98.4</td>
</tr>
<tr>
<td>CIV A/Canine/Florida/04</td>
<td>98.2</td>
</tr>
<tr>
<td>CIV A/Canine/Texas/04</td>
<td>98.0</td>
</tr>
</tbody>
</table>

Vaccination

Bacterial Pneumonia

**Definition**

- The colonization of pulmonary parenchyma by pathogenic organisms
- Characterized by:
  - influx of inflammatory cells (esp. neutrophils)
  - tissue destruction
  - loss of function
- Disease results from interaction of 1 or more agents (virus, bacteria) in a stressed or adverse environment
**BACTERIAL PNEUMONIA**

**PATHOGENESIS**
- The lower airways are normally sterile.
- Myriad defenses remove and destroy potential pathogens.
- Disease requires compromise of defense mechanisms.
- Immune defense compromised by:
  - Stress
  - Viral infections

---

**Streptococcus zooepidemicus** is the bacteria most commonly implicated in equine LRT

*Strep zoo*
- A universal URT commensal and most frequently isolated bacteria pathogen of equine LRT infections
- In the North American field efficacy study,* 373 horses had a pretreatment TTW
  - 259 animals (70%) had *Strep zoo* isolated from the pretreatment TTW
  - 208 had >1,000 colony forming units/mL
- A 2008 Canadian study evaluated >1,300 clinical equine cases for 6 years
  - *S. zooepidemicus* leading URT and LRT bacterial isolate of horses
  - Had 99% in vitro susceptibility to ceftiofur

---

If initial URT infection progresses—Abscesses, Interstitial & Pleural Disease
Treatment Modalities
- Directed at causative agent
- Directed at host's inflammatory /immune response
- Directed at enhancing pulmonary defenses/immunity
- Directed at secondary pathophysiologic processes

The Question?
- When were Antibiotics first discovered and when were they first used?

Impact of the accelerating use of antimicrobials
- Increased use corresponds to reduced efficacy, growing resistance
- 1928 – Alexander Fleming discovers penicillin
- 1945 – Widespread clinical use of antimicrobials begins; no reported resistance
- 2000 – Antimicrobial use is commonplace; non-judicious use frequently occurs, resistance is widespread
Why Worry about Antimicrobial drug use in horses?

Therapeutic decision making

- Often a difficult and complex process
- Often confusing and contradictory information (researchers, horse owners, websites & list serve’s)
- Frequently our decisions are based on:
  * Our last successful case
  * Our last failure
  * Our last case

Financial constraints? Diagnostic detail? Route of administration?

“Getting the drug into the horse??”

- Oral administration—many challenges...
- Absorption & tissue distribution determined by drug & species factors (most information defined in humans).
- Generally not ideal in horses
- Drug solubility; gastric pH, particle size, fluid volumes, feed in the stomach etc...
Few antimicrobials are approved for use in Horses

- The arsenal of injectable antimicrobials approved for systemic use in horses is limited
  - Ampicillin
  - Penicillin G (procaine)
  - Ceftiofur (Naxcel® sterile powder, Excede® sterile suspension)
  - Trimethoprim-sulfonamide

- Clinicians often resort to extra-label use of human drugs or those approved for other animal species.

Non-compliance is a leading cause of treatment failure

- Missed or late doses can result in:
  - Poor therapeutic response
  - Recurrence of infection
  - Bacterial resistance

- Compliance influenced primarily by convenience of protocol
- Key contributors to inconvenience: multi-dose regimens, longer treatment regimen

The greater the inconvenience of a treatment protocol, the worse compliance becomes

Beta-lactam antibiotics

- Penicillin- Procaine penicillin G, Na or K penicillin
- Synthetic penicillins- ampicillin, amoxicillin, ticarcillin
- Cephalosporins-
  - First generation- cefazolin, cephalixin
  - Third generation- ceftriax, ceftazidime
  - Fourth generation- cefepime
  - all have extended gm (-) activity
  - increased resistance to B-lactamase org.
- Most infections in horses caused by B-hemolytic strep. (uniformly susceptible to penicillins).
EXCEDE®
A New Sustained-Release Injectable Antibiotic for Horses

EXCEDE (ceftiofur crystalline free acid)
Sterile Suspension:
An equine-approved antimicrobial

**Indication** - Pfizer recently received FDA approval for use of EXCEDE® (ceftiofur crystalline free acid) Sterile Suspension in horses for the treatment of LRT disease caused by susceptible strains of *Streptococcus equi* ssp. *Zooepidemicus*.

**Dosage and administration** - Two IM injections at 6.6 mg/kg (3.0 mg/lb) 4 days apart. Therapeutic drug concentrations are maintained for a total of 10 days from initiation of treatment.

**Dose-volume equivalent** - Administered at 1.5 mL per 100 lbs bodyweight, with a maximum dose of 20 mL per injection site (≤10 mL per site is recommended).

When administered by an attending veterinarian, 2 doses of EXCEDE provide a full course of therapy and treatment compliance is assured.

EXCEDE is available in a ready-to-use 100 mL vial.

**The unique EXCEDE formulation**

Ceftiofur crystalline free acid (CCFA) is incorporated into a special oil base formulation

This formulation creates a depot of CCFA *in situ*

This depot gradually releases CCFA from injection site, thereby creating the sustained release effect
Systemic exposure to ceftiofur with EXCEDE vs. NAXCEL*

- **Approved EXCEDE dose**: IM at 6.6 mg/kg given 4 days apart (0 and 96 hrs)
- **Approved NAXCEL dose**: IM at 2.2 mg/kg daily for 10 days
- **Peak plasma concentration**:
  - EXCEDE $C_{\text{max}} = 1.01 \mu g/mL$
  - NAXCEL $C_{\text{max}} = 5.36 \mu g/mL$

**Key results:**

Total systemic exposure to ceftiofur is 2-fold higher with NAXCEL vs. EXCEDE

- EXCEDE $\text{AUC}_{(0-\infty)} = 157 \mu g\cdot hr/mL$
- NAXCEL $\text{AUC}_{(0-\infty)} = 353 \mu g\cdot hr/mL$ (once-daily IM dosing)

However, EXCEDE plasma concentration never drops below MIC (0.2 µg/mL)

Use of EXCEDE in juvenile horses

- **Current label**: EXCEDE not evaluated in horses <4 mos of age prior to licensing
- **University of California–Davis study**:
  - EXCEDE given SC to 6 foals 3–5 days of age
  - Label dosage given (6.6 mg/kg)
- **Results**:
  - Self-limiting diarrhea in 4/6 foals (onset 48–240 hrs)
  - No systemic adverse effects in any foal
  - No injection-site reactions
  - Ceftiofur and DFC metabolites reached mean therapeutic levels for target pathogens

Another question....

what is the pH of an equine stomach?
**Per Os in the Hoss**

- Gastric pH very variable (1.0 to 7.5) with periods of spontaneous alkalinization...
- Volume of fluids in GI tract; humans=5–10L per day total; horses=24L/day + 1.6L/hr of gastric, duodenal & pancreatic secretions
- Feeding- changes pH, alters gastric emptying and GI motility, > secretion of bile
- < oral absorptions noted with sulfa’s, doxycycline, rifampin, erythromycin

---

**Trimethoprim–Sulfonamide**

- Considered -cidal at high concentrations.
- Lipophylic and penetrates tissues well (CNS).
- Broad-spectrum coverage (gm (+), (-) and some anaerobes.
- Interfere with synthesis of folic acid from PABA with sulfonamides competitively inhibiting PABA.
- Purulent fluids rich in protein and PABA, this will decrease TMS activity.

---

**Trimethoprim–Sulfonamide**

- Good activity against many Strep organisms– although some resistance noted despite susceptibility results. (**
- Excellent GI absorption although reduced substantially by feeding....(delay feeding).
- Lack of clinical activity against anaerobes.
- 3.75g/50kg is the dose once a day No crushing tablets (as top dress)
Potentiated Sulfas

- $t_{1/2}$ = sulfamethoxazole 3.5–5 hrs.
- $t_{1/2}$ = sulfadiazine 3–4 hrs.
- $t_{1/2}$ = trimethoprim 2–3 hrs.
- BID PO dosing is necessary to attain therapeutic plasma concentrations of trimethoprim
  (Dowling in Bertone, 2004)

Trimethoprim–Sulfonamide

- Oral formulation containing TMP with sulfadiazine in a 1:5 ratio commonly dosed at 20 to 30mg/kg BID.
- In horses – rapid elimination of TMP leads to persistence of sulfonamide and changes optimal ratio. Therefore, potentiated sulfonamides should be dosed BID.

Newer Macrolides

- Pharmacokinetic advance over erythromycin.
- Azithromycin – high oral bioavailability. $T_{1/2} = 20$ hrs. Concentration in BAL cells $\pm 150 \times$ serum.
- Clarithromycin – more effective than azithro against *R. equi* in vitro. Improved efficacy in severe *R. equi* pneumonia as compared to erythro or azithromycin. (Giguere ACVM 2003)
- Tilmicosin – $T_{1/2} = 18$ hrs. $\pm$ against *R. equi*
**Tulathromycin Draxxin-Pfizer**

- New injectable macrolide for tx of pulmonary dz in cattle and swine
- Lung concentrations above MIC for 15 days for *P. multocida*
- Study in foals; 2.5mg/kg IM Q 7 days (#37 foals with lung abscesses)
- Results; tulathromycin well tolerated for tx of pulmonary abscesses in foals (NOT *R. equi*)
  - NB – very pH sensitive – strong distribution in lung tissue – inactive in acidic environments

**Gamithromycin (Zactran)**

- Initial studies (*in vitro*) are promising
- Investigated activity against *S. zooepidemicus* & *R. equi*
- 6 mg/kg IM (foals) maintained concentrations above MIC for both organisms for approximately 7 days

**Combination use of beta-lactams + aminoglycosides**

- Empirical treatment with a beta-lactam + an aminoglycoside often given
- Provides broad coverage, and potential synergistic effect
- Beta-lactam’s MOA is disruption of cell-wall synthesis
- Aminoglycosides have poor cell-penetrating ability
- Beta-lactam + aminoglycoside may have a potentially synergistic effect – beta-lactam degrades cell wall, allowing aminoglycoside to penetrate for a dual antimicrobial effect
**Antimicrobial associated diarrhea (AAD)**

- Most frequently observed AE of antimicrobial therapy
- Antimicrobials alter gut flora, allowing commensal enteropathogens (e.g., *C. difficile*) to proliferate
- 2009 study results*
  - >4,900 horses treated with antimicrobials for non-GI signs and presenting with diarrhea
  - Probable AAD diagnosed in 32 (0.65%)
  - Antimicrobials most commonly associated:
    - gentamicin n=12 (10 in combo)
    - enrofloxacin n=8 (1 in combo)
    - penicillin n=8 (8 in combo)
    - doxycycline n=6 (2 in combo)
  - AAD-associated mortality 6/32 (18.8%):
    - *C. difficile* (2), doxycycline (3), enrofloxacin (2), TMS (1)
- Conclusion: Any antimicrobial class can potentially cause AAD

*Reported at 2010 AAEP Annual Convention, publication pending, data on file, Pfizer Inc.

---

**Godzillacillin !!**

- Does ‘cutting edge’ medicine mean finding uses for the hot new drug in human medicine?
- The empirical use of enrofloxacin or vancomycin in horses is a **MAJOR** concern.
- Can we be effective stewards of public health and avoid regulatory action by FDA?

---

**Questions?**

mark.crisman@pfizer.com