Equine Infectious Respiratory Disease

Sandra D. Taylor, DVM, PhD, DACVIM
Purdue University
U.S. equine respiratory pathogens

- **24-month study** Pusterla et al, Vet Rec 2010
- Nasal swabs & blood submitted for PCR if signs of acute respiratory disease

![Pie chart showing percentages of different pathogens: Influenza 30%, EHV-1 11%, EHV-4 41%, S. equi 24%]
Review/update

- Influenza virus
- EHV-1, 4
- *Streptococcus equi* subsp *equi* (Strangles)
- *(Rhodococcus equi* – Dr. Balazs Toth)*
Influenza

• Orthomyxoviridae, RNA virus
• Type A
• 2 major surface proteins can mutate (antigenic variation) → drift
  – HA (hemagglutinin) binds host cell
  – NA (neurominidase) facilitates budding from host cell
Influenza

Epidemiology

• Based on HA and NA, divided into subtypes
  – 16 HA’s
  – 9 NA’s

• Horses:
  – H7N7 (subtype 1) ← last case in late 1970’s
  – H3N8 (subtype 2) ← current subtype worldwide
    • European lineage
    • American lineage
      – Kentucky
      – Florida
      – Ohio
      – Wisconsin

Different from one another (antigenic drift)
Influenza

Transmission

- Horses 2-3 years of age most susceptible
- Crowded, stressed
- Direct contact or airborne respiratory secretions
- Outbreaks within few days
  - Short incubation period (2 days)
  - High amount of virus in nasal secretions (x 6-7 days)
  - Cough helps spread
Pathophysiology

- Infects respiratory epithelium throughout tract → erosion of epithelium → inflammation, loss of mucociliary apparatus

- Takes at least 3 weeks for epithelium and cilia to regenerate
Clinical signs/pathology

• Clinical signs
  – High fever
  – Depression
  – Anorexia
  – Dry, hacking cough
  – Tachypnea
  – Serous $\rightarrow$ MP nasal discharge

• Clinical pathology
  – Lymphopenia
  – Monocytosis
Complications

- High mortality w/ viral interstitial pneumonia
  - Unvaccinated horses
  - Donkeys, mules

- Other complications
  - **Bacterial pneumonia**
  - Myositis
  - Myocarditis
  - Limb edema
Influenza

Perfect storm
Immune response

• Natural exposure
  – Humoral
    • Antibodies to HA and NA for ~ 4 months
      – Local (mucosal) IgA can neutralize virus and block entry
      – IgGa, IgGb opsonize to enhance phagocytosis
  – Cell-mediated immunity
    • T cells kill virus-infected cells

• Protected for 8-12 months against same isolate
**Influenza**

**Diagnosis**

- Nasopharyngeal swab
  - Culture (virus isolation)
    - Best when < 24 hrs
  - Directigen™ Flu-A
    - Stall-side
    - Abs to Type A on a membrane, add nasal secretions
  - PCR
    - Positive for up to 4 weeks

- Serology
  - 4x increase b/t acute and convalescent

- Thoracic radiographs
  - +/- Interstitial pneumonia, “aspiration” pneumonia
Treatment

- Symptomatic/supportive care
- NSAIDs
- Oseltamivir (NA inhibitor), 2 mg/kg PO BID
  - ↓ duration of signs and viral shedding
- Antimicrobials for 2° bacterial pneumonia
# Influenza Vaccines

<table>
<thead>
<tr>
<th>Brand</th>
<th>Manufacturer</th>
<th>Form</th>
<th>Route</th>
<th>Contents</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>FluAvert</td>
<td>Intervet</td>
<td>MLV</td>
<td>IN</td>
<td>Amer (KY)</td>
<td>q 6 mo (no series)</td>
</tr>
<tr>
<td>ProteqFlu</td>
<td>Merial</td>
<td>MLV, Canary pox</td>
<td>IM</td>
<td>Amer (KY), Europ (NM)</td>
<td>q 6 mo (3-series)</td>
</tr>
<tr>
<td>Calvenza</td>
<td>Boehringer Ingelheim</td>
<td>Killed</td>
<td>IN or IM</td>
<td>Amer (KY, OH), Europ (NM) +/- EHV-1,4</td>
<td>q 6 mo (3-series)</td>
</tr>
<tr>
<td>Fluvac Innovator</td>
<td>Pfizer</td>
<td>Killed</td>
<td>IM</td>
<td>Amer (KY), +/- EHV-1,4, EWT</td>
<td>q 6 mo (3-series)</td>
</tr>
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</table>

Additional boosters 2-3 weeks before show/sale/race

Equilis Frequenza®
Australian outbreak, 2007

- Influenza-free, not vaccinated
- 75,000 horses infected
  - < 100 deaths reported
- 60-100% infection rate in exposed horses
- H3N8, American lineage (Wisconsin/2003)
- Vaccination with ProteqFlu® (320,000 horses)
  - No signs if fully vaccinated prior to exposure
  - Vaccinated foals at 1 day of age
Equine herpesvirus-1, 4

- **Alphaherpesvirinae**
  - DNA virus
  - Enveloped, glycoprotein spikes

- **3 major syndromes**
  - Upper respiratory tract infection (EHV-1, EHV-4)
  - Abortion (EHV-1)
  - Myeloencephalopathy (EHV-1)
Pathophysiology

- Respiratory epithelium $\rightarrow$ local lymph nodes $\rightarrow$ lymphocytes (viremia) $\rightarrow$ uterus (abortion) or CNS (myeloencephalopathy)
- Infection within 1\textsuperscript{st} month of life $\rightarrow$ latent in trigeminal ganglion and lymphoid tissue $\rightarrow$ reactivation when stressed $\rightarrow$ reinfection of respiratory epithelium, etc.
EHV-1, EHV-4

- URT epithelium
- Lymph nodes
- CN5 ganglion

Shed x 3 wks

Mild URT disease
- Fever
- Nasal discharge
- Cough

Viremia

Cord endothelium

Vasculitis

Arthus rxn

EHV-1

Uterus

Abortion

Stress
Epidemiology

EHV-1

Non-neurotropic
- Abortion: 80%
- Mild URT disease: 20%
- ?

Neurotropic
- Neuro signs: 100%
- Mild URT disease: 65%
- Abortion: 35%
Clinical signs

- High fever
- Depression
- Anorexia
- Cough
- Serous nasal discharge
- +/- 2° bacterial pneumonia
- +/- neuro signs
  - Ataxia (hind > fore), urine dribbling, flaccid tail and anal tone
- +/- abortion
Immune response

• **Humoral**
  – Neutralizing antibody
    • Peaks 3 weeks after exposure
  – *Titers do not correlate with protection against neuro signs* Allen et al, AJVR, 2008

• **Cell-mediated immunity**
  – Probably most important, since intracellular (lymphocytes)
  – *Associated with protection against neuro signs* Allen et al, AJVR 2008
Diagnosis

- Nasopharyngeal swab
  - Culture (virus isolation)
    - Short window for live virus
  - PCR
    - Positive for up to 3 weeks

- Blood (buffy coat) PCR for EHV-1

- Serology
  - Can distinguish between EHV-1 and EHV-4
  - 4x increase between acute and convalescent
Treatment

- Symptomatic/supportive care
- NSAIDs
- Acyclovir
  - PO, poor bioavailability (2.8%)
  - IV, side effects, expensive, variable serum conc.
- Valacyclovir
  - PO, better bioavailability, but $$
  - Decreased severity and duration in Utah EHV-1 outbreak
- Antimicrobials for 2° bacterial pneumonia
## Vaccines

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<tr>
<td>Rhinomune</td>
<td>Boehringer Ingelheim</td>
<td>MLV</td>
<td>IM</td>
<td>EHV-1</td>
</tr>
<tr>
<td>Prestige</td>
<td>Intervet</td>
<td>Killed</td>
<td>IN or IM</td>
<td>EHV-1,4 +/- others</td>
</tr>
<tr>
<td>Calvenza</td>
<td>Boehringer Ingelheim</td>
<td>Killed</td>
<td>IN or IM</td>
<td>EHV-1,4 +/- flu</td>
</tr>
<tr>
<td>Innovator</td>
<td>Pfizer</td>
<td>Killed</td>
<td>IN or IM</td>
<td>EHV-1,4</td>
</tr>
<tr>
<td>Pneumabort-K</td>
<td>Pfizer</td>
<td>Killed</td>
<td>IM</td>
<td>EHV-1 (5x)</td>
</tr>
<tr>
<td>Prodigy</td>
<td>Intervet</td>
<td>Killed</td>
<td>IM</td>
<td>EHV-1 (5x)</td>
</tr>
</tbody>
</table>
Vaccine schedule

• Manufacturer recommendations
  – q 6 - 12 months after initial 3-dose series

**Not enough?**

Immunity short-lived: neutralizing antibodies decrease within a few months after vaccination

**Too much?**

Frequent vaccinations associated with increased neurologic form (Arthus)
Vaccine efficacy study

• Vaccinate → challenge with neuro form of EHV-1
  Goehring et al, Vaccine, 2010

• Vaccines did not prevent URT signs, viremia, or nasal shedding
  – No neuro signs in vaccinates or controls

• Rhinomune® better than Pneumabort-K® in:
  – Decreasing clinical sign severity
  – Decreasing nasal shedding (# horses and amount)
Recent EHV-1 outbreaks

• California
  – January 2012
    • Orange County, 11 horses (1 neuro)
  – September 2012
    • Tuolumne County, 8 horses (6 neuro)
    • Sonoma County, 3 horses (1 neuro)

• Utah → 10 states
  – May 2011
  – National Cutting Horse Association Western National Championships
  – 90 horses (33 neuro)
Streptococcus equi subsp equi

- Gram + cocci

- Lymphadenopathy

- Complications
  - GP empyema/chondroids
  - Internal abscessation (“Bastard Strangles”)
  - Purpura hemorrhagica
  - Myopathy
Epidemiology

• 1-5 yrs of age

• If first exposure, up to 100% morbidity
  – 8% mortality

• 4-5 yrs protection after natural infection

• Direct contact, fomites
  – Introduction of asymptomatic shedder (GP, sinus)
Strangles

Pathophysiology

Inhale or ingest

Nasal or buccal epithelium

Blood
Lymphatics

Lymphatics

Lymph nodes
- Replicates
- Neutrophil influx
Strangles

Virulence factors

• **HA capsule**
  – Resists phagocytosis from neuts
  – Necessary for SeM function

• **SeM protein**
  – Within cell wall
  – Resists phagocytosis from neuts and opsonization by macrophages
Clinical signs

- Fever
  - Incubation period = 2-6 days
- Depression
- Submandibular and/or retropharyngeal lymph node swelling
  - Rupture 7-10 days after onset of signs
- +/- MP nasal discharge
- +/- stridor, respiratory distress, dysphagia

Avg course = 23 days
Clinical pathology

- Neutrophilic leukocytosis
- Hyperfibrinogenemia
- Hyperglobulinemia
- Anemia of chronic inflammation

- Left shift, toxic neuts if 2° pneumonia
- Associated organ dysfunction if internal
Diagnosis

- Nasal swab, lymph node aspirate, GP wash
  - Culture
  - PCR for SeM protein
    - More sensitive
    - Detect asymptomatic carriers
    - Wild type vs. vaccine strain
Diagnosis

• Serology
  – Exposure, atypical signs
  – Antibodies to SeM protein
  – If > 1 : 400, likely infected
  – If > 1 : 1,600, at risk for purpura
  – If > 1 : 3,200, likely internal abscess or purpura
  – Does not differentiate vaccinates!
Diagnosis

Strangles

Fluid line

RP lymph node

Chondroids
Sequelae: 20% of cases

- GP empyema/chondroids
- Internal abscessation ("Bastard Strangles")
- Purpura hemorrhagica
- Myopathy
  - Manifestation of purpura
  - Rhabdomyolysis
- Complications increase mortality to 40%
Strangles

GP empyema

Rupture up through floor of guttural pouch

- Nasal discharge
- +/- chondroids
GP empyema

- Guttural pouch inflammation
  - Dysphagia
  - Facial paralysis
  - Head tilt

- Chondroid formation
  - Can shed for several months
  - Inapparent carrier
  - GP endoscopy/wash to test
Internal abscessation

- Antimicrobial use not proven to be risk factor
- Diagnostics
  - *Rectal exam
  - Transabdominal ultrasound
  - IP tap
  - CT
- Main differential = neoplasia
- Requires months of antimicrobial tx
- Mortality ~50%
Strangles

Purpura hemorrhagica

- Type III hypersensitivity (Arthus)
  - Ag (SeM)/Ab (IgA) complexes
Purpura hemorrhagica

• Re-exposure or vaccination
  – High titer may predispose

• Clinical signs
  – Edema → skin sloughing
  – Petechia/echymoses of mm
  – Internal vasculitis → severe/fatal
Purpura hemorrhagica

• Diagnosis
  – Skin biopsy
    • Leukocytoclastic vasculitis
    • PCR for SeM
  – SeM titer > 1 : 3,200
Myopathy

• Immune-mediated (purpura)
  – Ag/Ab complex deposition → vasculitis → muscle infarction

• Severe, acute rhabdomyolysis
  – Cocci and macrophages in muscle

• Signs/clin path
  – Firm muscle, stiff gait, colic
  – ↑↑ CK, AST

Sponseller, JAVMA, 2005
Strangles

Treatment

• Early disease (i.e. outbreak situation)
  – Fever, lethargy (lymph nodes still normal)
    • Antimicrobial treatment for 3-5 days
    • Prevents lymph node abscessation
    • Susceptible to re-infection

• Superficial lymphadenopathy
  – Drain lymph nodes
  – Antimicrobials unnecessary
    • Contraindicated??
Strangles

Treatment

• GP empyema
  – Systemic antimicrobials
  – Saline flush → local antimicrobials
    • Gelatin/penicillin
  – Recommend 3 PCR-negative GP washes to call truly negative

• Chondroids
  – Local acetylcysteine
  – Helical polyp basket (endoscopy)
Courtesy of Dr. Jennifer Dulin
Treatment

• Internal abscessation
  – Long-term antimicrobials
  – Average hospital stay = 2 weeks

• Purpura hemorrhagica/myopathies
  – Systemic antimicrobials
  – Dexamethasone
  – NSAIDs
  – Supportive care (IV fluids for rhabdomyolysis)
Antimicrobials

- Treatment of choice – B-lactams
  - Penicillins
  - Cephalosporins
- Sulfonamides (TMS)
- Others
  - Oxytetracycline
  - Chloramphenicol
  - Macrolides

- Examples for internal abscessation
  - Ceftiofur + rifampin x 1 month → TMS
  - K Pen x 1-2 weeks → chloramphenicol

Strangles
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<tr>
<td>Pinnacle</td>
<td>Pfizer</td>
<td>MLV</td>
<td>IN (non-preg)</td>
<td>Attenuated (no capsule) S. equi</td>
<td>q 12 mo (2-series)</td>
</tr>
<tr>
<td>Strepvax II</td>
<td>Boehringer Ingelheim</td>
<td>Protein extracts</td>
<td>IM</td>
<td>SeM protein</td>
<td>q 12 mo (2-series)</td>
</tr>
</tbody>
</table>

- Do not vaccinate if
  - Natural infection within previous year
  - Exposed during outbreak (check titer)
  - SeM titer > 1 : 1,600
Acknowledgements

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