Infectious Respiratory Disease in Horses

Age of onset: bacterial pathogens

**YOUNG**
- Perinatal
  - < 1 month
  - Gram negatives
  - Association with FPT
- 1-6 months
  - *R. equi* and *S. zooepidemicus*
  - Complete evaluation with TTW / culture / sensitivity testing

**ADULT**
- Long distance transport
- Following viral challenge
- Primary pathogen
  - *S. equi*
  - Strangles

Equine Viral Respiratory Disease

- Individual infection
- Co-morbid condition
- Equine influenza virus
- Equine herpesviruses
  - EHV-1
  - EHV-4
  - EHV-2
  - EHV-5
- Equine adenovirus
- Equine rhinovirus B
- Equine rhinovirus A

Pusterla et al, Veterinary Record March 23, 2013
Foal pneumonia

- < 1 month
  - Sepsis
  - FPT
    - Hematogenous
    - Ascending via omphalophlebitis
  - G-neg > G pos
    - E. coli, Klebsiella, Actinobacillus, Salmonella, Strep.
    - Aspiration of meconium inactivates surfactant
    - Inflammation: TNF-alpha, interleukin-beta, IL-8
    - Edema and vasoconstriction result
    - Decreased type II pneumocyte function = reduced surfactant
    - Viral: EHV-1/4, EVA, adenovirus (immunodeficiency), EIV A

Foal Pneumonia

- 1 month to 6 months
- *S. equi* zooepidemicus and *R. equi*
- Anaerobes uncommon
- Respiratory viruses are uncommonly a primary invader in nursing foals
- Adenoviruses (EAdVs) have been investigated and are ubiquitous along with EHV-2.
  - Immunocompromise (Arabian foals / SCID)
  - EHV-2 may be a predisposing cause of *R. equi*

Interstitial pneumonia

- Bronchointerstitial pneumonia
- Also termed:
  - Acute lung injury
  - Acute respiratory distress syndrome
- Foals 1-6 months of age
- Respiratory distress
- Tachypnea
- Fever
- High mortality
Loss of architecture

[Image of horse]

[Image of tissue sample]
• Typically an individual case
• Severe respiratory distress
• Hypoxemia, hypoxemia, respiratory acidosis
Acute lung injury

- Severe pulmonary trauma caused by physical or chemical injury or by exaggerated pulmonary immune response.
- Acute onset, bilateral pulmonary infiltrates.
- A ratio of pulmonary arterial oxygen pressure (Pa02) to fraction of inspired oxygen (Fi02) < 300 for ALI (less severe) and < 200 for ARDS.
- No consensus for veterinary medicine.

Diagnosis

- Rule out infectious disease
- Severe *R. equi* pneumonia looks very similar
- Respiratory distress
- Cyanosis
- Hypoxemia
- Leukocytosis with hyperfibrinogenemia

Treatment

- Mechanical ventilation is used in human medicine.
- Other than equine neonates, nasal insufflation of humidified oxygen will be the primary means of therapy.
  - Unilateral, bilateral or tracheal.
- Antiinflammatory therapy
  - CCS
    - Dexamethasone (0.05-0.2 mg/kg daily – BID)
    - Methylprednisolone (Solu-Medrol) 2 mg/kg IV as a loading dose
  - Then 2 mg/kg IV daily, divided into 4 doses; or 0.5 mg/kg IV QID.
Clinical Management

• Bronchoconstriction is not significant
  – Pulmonary edema clearance is mediated by Beta 2 receptor activation, albuterol or clenbuterol may provide benefit for this reason.
  – Bronchodilation may potentiate V/Q mismatch, deterioration will indicate that therapy should be modified / discontinued.
• Judicious use of IV fluids may be indicated, over hydration should be avoided.
• Hypovolemia reduces oxygen delivery (reduced CO) CVP should be monitored to determine fluid needs.
• Nutrition should also be carefully addressed.

• Free radical scavengers
• Vasodilator therapy
• Overall prognosis is guarded: 60-69%
• Survival is associated with excellent pulmonary function.

Rhodococcus equi (R. equi)

• Gram positive
• Facultative intracellular pathogen
• This bacterium is present on (nearly) all farms
• Disease in endemic on some, not all farms
  – High morb / mort when present
  – 3 weeks to 5 months of age
VapA = virulence

- Sequencing of large plasmid in 2 isolates
- 3 functional regions
  - 2 of the 3 regions
    - Plasmid replication stability
    - Segregation
  - The 3rd region of the plasmid = pathogenicity island
    - 23 kb
    - Certain genes that encode for VAP proteins
- Eight virulence associated proteins (VAP)
  - VapA and VapC to VapI
    - VapA and VapC are non-functional
  - Signal sequence indicating extracellular proteins
  - VapA is surface expressed and temperature regulated
    - 34-41°C
    - VapA alone is necessary, but not sufficient for pathogenicity
  - VapC, D and E are secreted and temperature regulated
• Chronic bronchopneumonia
• Extensive abscess formation
• Slow progression
• Marked pulmonary reserve
• Early diagnosis can be challenging
• Early
  – Respiratory distress with exercise
• Chronic
  – Reduced appetite, fever, labored breathing
Diagnosis

• TTA culture positive
  – Presence of VapA gene = VapA
  – Amplification of gene via PCR
• PCR must be in conjunction with culture (not a replacement for culture).
  – Identify other pathogens
  – Determine antimicrobial susceptibility
• TT/BA sample from:
  – Foal with clinical evidence of pneumonia
  – Cytology from TBA supports sepsis
  – Radiographs / ultrasound that support R. equi
Extrapulmonary disorders

- Ex = osteomyelitis, abdominal abscess
  - Intestinal lesions in ~ 50%
- Definitive through culture + PCR (vapA)
- Suggestive due to dx of R. equi and inaccessible site in a TBA R. equi (vapA) positive individual
  - Uveitis or polyarthritis (30%)
  - Synovitis = non-spetic, mononuclear pleocytosis,
- GIT is problematic
  - Culture positive (feces) is not confirmatory for R. equi
  - Few (4%) will only have GIT dz
• Rare EPD:
  – Panophthalmitis
  – GP empyema
  – Sinusitis
  – Pericarditis
  – Hepatic
  – Intracranial

Evidence behind culture of TBA

• Overall 69% sensitivity for culture
• Presence of organism is possible from environmental contamination (aerosol)
  – 35% on one farm with endemic disease (Ardans AAEP Proc. 1986)
• Other pathogens can also be identified

Treatment

• Macrolide with rifampin
  – In vitro activity, PK data, retrospective evidence (moderate evidence)
• Evidence to support resistant strains provides a more guarded prognosis (Giguere JAVMA 2010)
• Clarithromycin > azithromycin > erythromycin
  – Clarithromycin-rif better for severely affected foals
  – NO random assignment for this study
• Erythromycin
  – Less bioavailable
  – Fasted (x 4) to enhance absorption
• Rif decreases ML absorption?
  – Suggestion (with evidence) by Peters et al (2011) and Venner (2010). Until this evidence is present to
demonstrate that ML w/out rif is as efficacious as ML + rif
the recommendation of combination therapy remains
canstant (Giguere 2013).

Potential complicating factors

• Diarrhea
  – Generally self limiting in foals
• Hyperthermia and tachypnea
  – Definitively demonstrated w/ erythro, suggested
with newer generation agents
• Diarrhea in mares

Foals infected with resistant strains

• TX and FL, 4% were resistant
• When present 7X greater chance of death
• Misclassification of resistance is possible
• Treat based on susceptibility
  – Doxycycline 10 mg/kg PO BID + rif
  – Chloramphenicol 50 mg/kg PO QID (human
  health)
  – TMS 30 mg/kg PO BID-TID + rif
Ancillary therapy

- Humidified oxygen
- Immune-mediated polysynovitis, resolves with effective treatment of primary disorder
- Local septic arthritis / osteomyelitis specific treatment is required
- Abdominal abscess formation carries a poor prognosis

Foals with subclinical disease treated with ML+rif compared with placebo treatment did not have an increased recovery rate, suggesting that spontaneous resolution is likely in subclinically affected foals, regardless of treatment protocol


Hyperimmune Plasma

- VapA and vapC hyperimmunized individuals similar to R. equi.
- Should not use plasma that is not R. equi
- HIP licensed plasma is recommended over plasma obtained from R. equi immunized horses.
  - Potency, purity and safety
  - 1 L not later than 48 h
  - Commonly, 2nd dose 2-4 weeks of age
  - With surveillance
Strangles

*S. equi*

- *Streptococcus equi* subsp. *equi* (Lancefield group C)
- Primary infection of the oropharynx
- Local and regional LN
- Progression to fever, lymphadenopathy, purulent nasal discharge and abscess formation.
• Abscess drainage generally occurs to the external skin surface or through the auditory canal (guttural pouch)
• Tracheal compression can be severe and life-threatening
• Submandibular / retropharyngeal most common
• Others: (tracheo)bronchial ln, abdominal / mesenteric ln, and brain.

• Bacterial survival in the environment is limited
• An important reservoir for the bacteria is the carrier status
• Serious complications develop in ~ 20% of cases with case fatality rate ~ 8%.
  − S. equi consensus statement 2005 Sweeney et al.

• S. equi gains entrance through the mouth and/or nose
• Cells of the lingual and palatine tonsils and follicular epithelium
• No colonization before penetration
• Within hours, hard to detect on mucosal surface, but can be found within epithelial and subepithelial cells
• Translocation to regional lymph nodes
• Regional localization of PMNs to site
• Abscess in 3 to 5 days once S. equi enters lymph node.
• PMNs cannot kill bacteria
  – Hyaluronic acid capsule
  – SeM has antiphagocytic properties
  – Mac protein
  – Others

• Bacteria can be disseminated elsewhere
  – Hematogenous
  – Lymphatic
• Bastard / metastatic strangles

**Disease Transmission**
• Nasal shedding 2-3 days post initial fever
• Shedding can continue 2-3 weeks
• Most (75%) horses have long-lasting immunity post infection
• Older horses typically have more mild disease d/t residual (memory) immunity.
• Still shed and can serve as risk to susceptible individuals.
• Foals that ingest colostrum from immune mares are considered protected until ~ weaning.
Transmission

- Direct
- Indirect
- Transmission from healthy appearing horses
  - Incubating disease
  - Recovering, but still shedding
  - Prolonged shedding
    - Chondroid

Survival in Environment

- Consider all factors.
- Current evidence has demonstrated may approach 30 days.
- Shorter with season and direct sunlight.
- Winter provides survival advantage in UK.
  - Weese et al CVJ 2009
  - Durham et al EVJ 2018

Diagnosis: GP secretions via endoscopy

- Culture
  - Nasal exudate
  - Purulent material
  - Nasal swab
  - May be negative early
    - Sens.
- PCR
  - SeM gene encoding antiphagocytic M protein
  - Dead or alive
  - PCR inhibitors
    - Should accompany culture
- Serology
  - Ab production against SeM
Vaccination

- Extract vaccine
  - 7-10 days for immune response.
  - Annual booster.
  - Do not vaccinate if infected within previous year.
  - Do no vaccinate in face of outbreak.

- Modified live vaccine
  - Induction of mucosal immunity.
  - Live, attenuated.
  - Healthy, afebrile horses.
  - 2 doses 2-3 weeks apart.
  - Do not administer during an outbreak.
  - Do not administer to < 6 month old horses.

Control of Outbreak

- Stop movement of horses
- Separate infected / sick from healthy.
- Carriers are best detected with GP (endoscopy) sampling.
  - qPCR testing
- Negative on consecutive tests = clean.

- Source? Examine healthy horses that are positive on culture / PCR, perform GP endoscopy.
- Strict isolation from healthy and infected / sick.
- Temp. all, at first fever penicillin x 5 days.
  - No immune induction, still susceptible.

Adapted from Boyle et al ACVIM Revised consensus 2018
**Clinical Management**

- Facilitate drainage
- If needed, surgical drainage.
- Avoid antibiotics unless complicated case.

- Complicated case:
  - Persistent fever
  - Tracheostomy
  - Metastatic abscess
  - PH and CCS therapy

  - Penicillin is drug of choice.
  - Other options.

**Complications**

- Approx. 20% cases
- Metastatic lesions
  - Pulmonary
  - Peritoneal
  - Renal
  - CNS
- Immune mediated disease
- Others
  - Glomerulonephritis

- Persistent infection within GP
  - Chronic infection
  - Additional sites of dissemination
    - Myocarditis
    - Endocarditis
    - Panophthalmitis
    - Periribital abscess
    - Ulcerative keratitis
    - Paravertebral abscess
    - Septic arthritis
    - Tenosynovitis
Immune Mediated Disease

- Purpura hemorrhagica
- Aseptic necrotizing vasculitis
- Edema and petechiation
- Immune complex disease among blood vessels
  - High antibody titer at the time of exposure
    - Natural
    - Vaccine
- Muscle involvement
  - Muscle infarction
    - Coagulative necrosis of muscle with infarctions
  - Myositis
    - Rhabdomyolysis with progressive atrophy
    - Immune mediated
    - QH predilection
- Muscle involvement

Other Complications

- Myocarditis
- Glomerulonephritis
- Agalactia in pregnant brood mares, not associated with mammary infection.

Bacterial Pneumonia

- Viral
- Secondary invaders
- Long distance
- Stress
- Co-mingling

Pleuropneumonia

- Pyrexia
- Lethargy
- Exercise intolerance
- Long distance transport and clinical signs
- Abnormal auscultation, particularly with disease progression.
- To rebreathe or not rebreathe?
  - Increased inhaled CO2
  - Deeper breaths
Clinical Management of Pleuropneumonia

- Physical examination
- Ultrasound
- Thoracocentesis
- Thoracic radiographs
- Transtracheal wash
- Antimicrobial selection
- Hematology
- Long term plan?
Pathogens of Concern

- *Streptococcus equi var zooepidemicus*
- *Pasturella* spp.
- *Actinobacillus* spp.
- *E. coli*
- *Klebsiella pneumoniae*
- Anaerobes
  - *Bacteroides* spp.
  - *Clostridium* spp.

Antimicrobial Selection
Continued Therapeutics

- Clinical management for infectious disease
- Broad spectrum antimicrobials 2-4 weeks
- Removal of focus of sepsis is key
- Rarely prolonged management
  - Recurrence of fluid
  - Persistent sepsis
- Overall favorable prognosis following thoracotomy
  - Survival and performance