Potomac Horse Fever

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Lecture outline

• Review
  – Complex life cycle of intermediate hosts
  – Literature review
  – Pathophysiology
  – Clinical signs
  – Dx/Tx/Prevention

• Retrospective study
  – Purdue University & Hagyard Equine Medical Institute
Etiology

• *Neorickettsia risticii*
  – Formerly *Ehrlichia risticii*
    • “Equine Monocytic Ehrlichiosis”
  – Gram negative, obligate intracellular bacteria
  – Infects monocytes/macrophages, GI epithelium

• Related pathogens
  – *N. helminthoeca*
  – *N. sennetsu*
History

• 1979: horses on pasture along Potomac River
• Currently 43 states, Canada, S. America, Europe
Life cycle: *N. risticii*

- Reservoir = trematodes (flukes)
  - *N. risticii* infects trematodes
    - *Acanthatrium sp.*
    - *Lecithodendrium sp.*

- Vertical transmission in trematode
  - Adult to egg

- Horizontal transmission to bats/birds
  - Reservoir for trematodes
Life cycle: trematode

- Intermediate hosts of trematodes = snails and aquatic insects
  - Trematodes mature in snails → ingested by larval stages of aquatic insects

Snail: *Juga sp.*

Caddisfly

Mayfly

Dragonfly
Life cycle: trematode

1. **Metac**
   - Bat/bird eats insect

2. **Aquatic insect eats cercariae**

3. **Cercariae**
   - (Cercaria $\leftarrow$ Sporocysts)

4. **Snails**
   - Penetrates snail foot

5. **Ciliated miracidia**

6. **Egg in feces**

7. **Adult**
   - Sexual repro

8. **Bat/bird eats insect**

9. **Metac**
Life cycle: trematode

Metacercariae

Adult

Sexual repro

Egg in feces

Ciliated miracidia

Penetrates snail foot

Snails

(Cercaria ← Sporocysts)

N. risticii

Aquatic insect eats cercariae

Bat/bird eats insect

Cercariae

N. risticii
Ingestion by horse

Metacercariae

Aquatic insect eats cercariae

Cercariae

H₂O source

Hay

Pasture

N. risticii
Literature review

• Described as “Acute Equine Diarrhea Syndrome” (Knowles, 1984)

• IV transfusion of blood from clinical horse to normal horse resulted in disease (Whitlock, 1984)

• Serological evidence of rickettsial bacteria (Rikihisa 1984)
  – Serum (antibodies) from affected horses reacted (bound) to *Ehrlichia sennetsu* (*N. sennetsu*)

• Named *Ehrlichia risticii* (Holland, 1985)
### Literature review: classification

<table>
<thead>
<tr>
<th>ORDER</th>
<th>Rickettsiales</th>
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<tr>
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<td></td>
<td>• E. risticii</td>
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<td>• E. canis</td>
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<td>• E. chaffeensis</td>
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<td>Rickettsia</td>
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<td>• R. rickettsia</td>
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Literature review: oral transmission

• 8 ponies housed with infected ponies did NOT become infected

• 8 ponies fed feces (NG tube) from infected pony → 1 became infected

• 13 ponies fed *N. risticii* (NG tube or drench) → 9 infected

Palmer, Benson, JVIM, 1994
Literature review: immune escape

- *N. risticii* strains differ in surface proteins and structure
  - Antigenic variation due to mutations in > 9 outer membrane proteins
    → ineffective vaccine!
  - Strains cluster in regions and time periods
  - Some packed into dense morulae, some found individually in cytoplasm

Chaichanasiriwithaya et al, J Clin Micro, 1994
Wen et al, Intl J Sys Bact, 1995
Biswas et al, Inf and Immun, 1998
Vemulapalli et al, Micr Path, 1998
Gibson et al, Vet Res, 2011
Literature review

• Snails from stream in northern California
  – *Juga yrekaensis*
  – 10/80 contained trematodes with *N. risticii*

• Injected infected trematodes (cercaria) SQ into 2 horses

Barlough et al, Appl Envir Micro, 1998
Pusterla et al, J Clin Micro, 2000
Literature review

Day 0

Day 18

Day 21

Day 28

Blood

SQ

Blood

Blood

Blood

Blood

Macrophages

Pusterla et al, J Clin Micro, 2000
Literature review

Results: (for each color, 1 line = 1 horse)

Feces PCR +

Blood PCR +

Clinical signs

Ab titers range from 1:40 – 1:160
Literature review

Electron micrograph of *N. risticii* organisms in vacuole of tissue culture macrophage

Pusterla et al, J Clin Micro, 2000
Literature review

- Experimental exposure to *N. risticii*

  Skin penetration? 
  Ingestion?

  Stood in water with *N. risticii*-infected cercaria
  Drank water with *N. risticii*-infected cercaria
  Fed flies infected with cercaria/*N. risticii*

Madigan et al, EVJ, 2000
Ingest insect/trematode/N. ristcii

Insect/trematode not pathogenic

N. ristcii infects colon crypt cells, macs & mast cells

Inflammation/mucosal damage

Translocation of G- bacteria

Endotoxemia/SIRS

~30-40%

Bacteremia (N. ristcii)

Infected monocytes
Pathophysiology

- End result:...

↓ absorption of Na⁺ and Cl⁻ → water stays in lumen

↑ secretion of Cl⁻ → Na⁺ and water follow

Watery diarrhea
Clinical signs

• Biphasic fever
  – 2-4 days post-infection (usually undetected)
  – 10-14 days post-infection
• Anorexia
• Mild colic
• Profuse, watery diarrhea
• Dehydration/hypovolemic
• Laminitis
• +/- “toxic” gums, tachycardia (SIRS)
• +/- edema
Clinical signs

• May see laminitis before diarrhea!
  – Front feet or all four
  – Reluctance to move
  – Sweating, tachycardia

• Not all have diarrhea
Clinical signs

• Delayed abortion
  – Occurs in ~50% of infected, pregnant mares
    • Long et al, AJVR, 1995
  – 2-3 months after clinical signs
    • Systemic infection in fetus
      – Colitis, lymphadenitis, myocarditis, hepatitis
      – PCR positive
  – If clinical disease and don’t abort, foal is normal
Clinical pathology

- Leukopenia
  - Neutropenia ➔ Into gut wall or 2° to bacteremia
  - Degenerative left shift

- Polycythemia
- Hyperlactatemia
- Hypoproteinemia
- Hypoalbuminemia

Protein-losing enteropathy
Differential diagnoses

- Salmonellosis
- *Clostridium difficile*
- *Clostridium perfringens* Type A (enterotoxin)
- Toxins
  - Cantharadin (Blister Beetle)
  - NSAIDs (right dorsal colitis)
Laminitis

• Is pathophysiology of laminitis different from other causes of colitis?? Probably NOT
  – Ciprofloxacin study Yamarik et al, J Vet Pharm Ther, 2010
    • All horses developed colitis
    • 50% developed laminitis
    • Negative for *C. difficile* or *C. perfringens*
    • 30% developed laminitis
Diagnosis: history

• Proximity to river
  – Even if not drinking river water, flies still around

• Barn lights

• Summer/fall
  – Hot weather triggers release of cercariae by snails
Diagnosis

• Serology
  – Immunofluorescence assay (IFA) or ELISA
    • Many false positives
      – Exposure (not necessarily disease)
      – Vaccines
    • False negatives
      – Some horses have poor immune response (low titer)
  – Helpful if....
    • 4x increase in titers between acute and convalescent
      – But most have already seroconverted when show signs
    • High titer + signs + NO vaccine (> 1:2,560)

Not blood smear!
Diagnosis

• PCR blood, feces
  – Will detect DNA from live or dead organisms

• Culture
  – Not as common since PCR available
  – Used in research settings to obtain electron microscopy images

Foot rads

Courtesy Dr. Jose Mendez
Treatment

• Oxytetracycline
  – 6.6 mg/kg IV BID x 5 days
  – Up to 15 mg/kg IV x 5 days
• NSAIDs
  – Inflammation of gut, lamina
• Supportive care
  – Correct hydration
    • IV fluids
  – Colloids
• Ice feet, deep bedding
Treatment

- Endemic area + summer + no hx of antimicrobial use + signs $\rightarrow$ start oxytet before definitive diagnosis?

- **Yes**, if well-hydrated
  - Oxytet can be nephrotoxic

- **BUT** keep in mind, many infected horses recover without oxytet
  - Sequelae are often more dangerous than PHF
Necropsy: colon

• **Gross**
  – Variable lesions, usually mild
  – Predominantly colonic edema/mild ulceration
    • Right dorsal colitis may be 2° to NSAID administration
  – Small colon affected to lesser extent

• **Histopathology**
  – Degenerated/blunted colon epithelium, ↓ goblet cells
  – Infiltration of lymphocytes, plasma cells and macrophages in colonic submucosa
Prevention

• Fly control
  – Turn off barn lights
• Keep water sources clean
• Molluscicides
• Vaccination?
Vaccines

- *E. risticii* bacterin
  - PHF-Vax® (Schering-Plough/Merck) OFF MARKET
  - PotomacGuard® (Fort Dodge/Pfizer) OFF MARKET
  - PHF-Gard® (Pfizer) OFF MARKET
  - Equine Potomavac® (Merial)
    - 1 strain? (used to be before merger)
Vaccination

• May ↓ incidence and disease severity
• Protection short-lived
  – Vaccinate q 4-6 months (fly season)
    • i.e. March, July

Courtesy of Glenwood Veterinary Clinic
Retrospective study

- 15 year period (1996 – 2011)
- Medical record retrieval
- Inclusion criteria
  - Diagnosis → at least one of the following:
    - PCR positive (blood or feces)
    - IFA titer $> 2,560$ in non-vaccinated horse with signs
    - 4-fold increase between acute and convalescent titers
Retrospective study

• 50 cases
  – Purdue University: n = 26
  – Hagyard Equine Medical Institute: n = 24
Retrospective study

• Objective
  – Descriptive (signalment, clinical signs, laboratory values, treatment, survival status)
  – Identify predictors for survival

• Median age = 7 years
• Age range = 4 months to 29 years
• No gender predilection
• No breed predilection
Retrospective study: history

- Most common presenting complaints
  - Diarrhea
  - Colic
  - Fever
  - Anorexia
  - Depression
Retrospective study: history

• Prior to presentation at referral hospital:
  – 62% received Banamine
  – 34% received antimicrobial OTHER THAN oxytet
  – 6% received oxytet

• Median duration of illness prior to presentation = 5 days
Retrospective study: vaccine hx

• Only 17 had known vaccine history
  – Of those, 59% were previously vaccinated for PHF
    • Brand not determined

• Only 9 of 17 had documented vaccine date
  – All within previous 5 months
    • 1 within last month
    • 1 within last 2 months
    • 2 within last 3 months
    • 4 within last 4 months
    • 1 within last 5 months
Retrospective study: physical exam

• Clinical signs
  – Diarrhea  66%
  – Fever    48%
  – Anorexia 42%
  – Depression 40%
  – Colic    38%
  – Lameness 18%
Retrospective study

• Laminitis
  – Confirmed in 26%
    • Based on radiographs
  – Suspected in 36%
    • Based on lameness/reluctance to walk, +/- radiographs
  – 78% of the lame horses were lame in all 4 feet

Courtesy of Dr. Ramiro Toribio
Retrospective study: diagnostics

• Serology
  – Performed at least once (acute) on 19 horses
    • Median acute IFA titer = 1:640
    • Median convalescent IFA titer = 1:1,280
• Blood PCR
  – Performed on 40 horses
    • 83% were positive
• Feces PCR
  – Performed on 16 horses
    • 75% were positive
Retrospective study

• Median hospital stay = 6 days
• 76% survived to discharge
  – PCV and BUN/creatinine significantly higher in non-survivors (p < 0.01)
  – Sodium and chloride significantly lower in non-survivors (p < 0.01)

• Independent factors associated with survival
  – Chloride
  – Oxytet administration
Conclusions

• PHF is common cause of equine diarrhea in Midwest

• Limited vaccine efficacy, but worth giving

• Severity of colitis is best predictor of survival
  – NSAIDs may exacerbate primary PHF

• Treatment with oxytetracycline early in disease may improve survival rate
Acknowledgements

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  – Dr. Balazs Toth
  – Dr. Jennifer Dulin
Retrospective study: history

• Most common presenting complaints
  – Diarrhea 40%
  – Colic 26%
  – Fever 22%
  – Anorexia 4%
  – Depression 2%