The *Ehrlichia*, *Anaplasma*, *Borrelia*, and the rest....

Southern Region Conference to Assess Needs in IPM to Reduce the Incidence of Tick-Borne Diseases

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Rickettsia

- The known pathogens
  - Chris Paddock
    - *R. rickettsii*
    - *R. parkeri*
  - Kevin Macaluso
    - *R. amblyommi*
    - *R. felis*

- The potential pathogens

- Next 30-40 min
  - The rest: *Ehrlichia, Anaplasma, Borrelia, etc.*
The most common suites of tick-borne pathogens of humans in the Southern US

- **Amblyomma americanum** (lone-star tick)
  - *Ehrlichia chaffeensis*
  - *Ehrlichia ewingii*
  - *Ehrlichia sp. PME agent*
  - ?? *Borrelia lonestari*
  - ?? *Rickettsia amblyommi*
  - ?? *Bartonella spp.*

- **Ixodes scapularis** and *I. pacificus* (black-legged ticks)
  - *Babesia microti*
  - *Borrelia burgdorferi*
  - *Anaplasma phagocytophilum*

- **Dermacentor variabilis**
  - *Rickettsia rickettsii*

- Others ticks ()
  - *Babesia* divergens-like species
  - *Babesia sp. WA1* (California)
  - Relapsing fever *Borrelia* spp.
  - ?? Relapsing fever borreliae in Florida canines
A. americanum: King of the South...and expanding its grasp

Up to about 1999

Current...maybe...
Established* and reported** distribution of the Lyme disease vectors Ixodes scapularis (I. dammini) and Ixodes pacificus, by county, United States. 1907-1996

*at least 6 ticks or 2 life stages (larvae, nymphs, adults) identified.
**at least 1 tick identified.
Factors that influence distributions of TBD

- Vectors
- Hosts
- Humans
  - Change in behavior, activities
  - Aging population, etc.

**COMPLEX INTERACTIONS**

- Habitat
  - Fragmentation
  - De/Reforestation
  - Suburbanization
  - Flood potential

- Climate
  - Temperature
  - Precipitation
  - Humidity
Trend: Increase in Tick-borne Diseases

CDC, MMWR

Lyme Disease: 2006 alone – 19,931 cases

Rocky Mtn SpFeV: 2006 alone – 2,288
WTD distribution and density
WTD distribution and density

1999
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Pathogens of Humans

Order Rickettsiales
Family Rickettsiaceae

Family Anaplasmataceae

Pathogens of Humans and found in the USA

- Ehrlichia muris
- Ehrlichia chaffeensis
- Ehrlichia ewingii
- Ehrlichia canis
- Ehrlichia ruminantium
- Ehrlichia sp. P-Mtn
- "Candidatus Neoehrlichia lotoris"
- "C. Neoehrlichia mikurensis" Nagano21
- "C. Neoehrlichia mikurensis" Germany Human
- Anaplasma phagocytophilum
- Anaplasma marginale
- W. pipiens
- W. endosymbiont of Brugia malayi
- "C. Xenohaliotis californiensis"
- N. sennetsu
- N. helminthoeca
- O. tsutsugamushi
- R. typhi
- R. prowazekii
- R. montanensis
- R. parkeri
- R. amblyommii
- R. rickettsii
- "C. Nicolleia massiliensis"
- "C. Midichloria mitochondrii"
- H. obtusa
Ehrlichia chaffeensis

- Predominate ehrlichiae in humans in the South
- White-tailed deer is principal reservoir
  - Coyotes, red fox, raccoons, dogs, and lemurs
  - Rodents appear unimportant
Deer studies

- Long-term infections
- Naturally and experimentally susceptible to multiple strains

Davidson et al., 2001; Yabsley et al., 2003, JCM; Varela et al., 2005; VBZD
29% of 7,673 deer seropositive

Dawson et al., 1994
Irving et al., 2000
Mueller-Anneling et al., 2000
Yabsley et al., 2003
E. chaffeensis surveillance using deer as sentinels

Yabsley et al., 2005; AJTMH
Ehrlichia ewingii

- Lone star tick is only proven vector
  - Others?

- Causative agent of canine granulocytic ehrlichiosis
  - First detected in 1969, but not described until 1992

- First reported human cases were in 1999
  - Flu-like illness without rash in humans

- Has never been cultured
Ehrlichia ewingii

WTD as Reservoirs?

Antibodies detected by ELISA in multiple populations - associated with LST and E. chaffeensis presence

13 of 259 (5%) WTD from 6 states PCR positive

Yabsley et al., 2002 EID

Yabsley et al., in prep.
Discovery of PM

*Ehrlichia* sp.

- Person at Panola Mountain State Park near Atlanta, GA became host for an *A. americanum* nymph
  - Sore neck developed 9 days later
  - Generalized pain prevented sleep
  - Put on doxycycline for 10 days
    - Rapid improvement of clinical signs in 48 hrs
  - Blood sample PCR positive for PM *Ehrlichia* sp.

Reeves et al., 2008 J Med Case Reports
Natural History of PM *Ehrlichia* sp.

Loftis et al., 2008, *Vet Microbiol*

Yabsley et al., 2008, *JWD*

Loftis et al., 2008 *BMC Infect Dis.*

36 of 3,799 ticks positive from 10 states

PCR-positive deer

PCR-positive ticks

PCR-negative ticks
Two genotypes of PM Ehrlichia sp. present in US based on analysis of map1 gene

Loftis et al., 2008
BMC Infect Dis.
*Ixodes scapularis*

“black-legged tick”
Anaplasma phagocytophilum

- Infects a wide range of hosts in US, Europe, and Asia
- Genetically and biologically diverse species

- In US two predominate genetic types are the AP-Var1 and Human variant (Ap-ha)
  - Other minor variants detected in upper Midwest
Anaplasma phagocytophilum

- Ap-ha associated with human and rodent/other wildlife infections in NE and upper Midwest

- Ap-Var1 associated with WTD infections and not rodents or raccoons
  - Experimentally and in field

(Massung et al., 2003; Massung et al., 2005; Dugan et al., 2006; Reichard et al., 2008; Yabsley et al., 2008)
Anaplasma in dogs

National prevalence: 4.7%
Almost 1 million dogs tested
Anaplasma in WTD

- 15 PCR-positive WTD were all infected with Ap-Var1
- Four variants based on p44 gene sequences

Antibodies reactive with Ap present throughout WTD populations in Southeast (and Northern states as well)

All strains should cross-react serologically

Dugan et al., 2006 VBZD
Anaplasma phagocytophilum

Differences in North vs. South?
- Few human cases in the Southeast
  - 2006
    - New England, Mid. Atlantic, and N. Central – 613 cases
    - Southeast – 31 cases
- Raccoons
  - Reservoirs of Ap in CT \( \text{(Levin et al., 2002)} \)
  - All raccoons tested in South are negative \( \text{(Dugan et al., 2004; Yabsley et al., 2008)} \)
  - Experimentally, raccoons develop long term infections with Ap-ha but short-term infections with Ap-Var1 \( \text{(Yabsley et al., 2008)} \)
Much confusion on *Borrelia* in the Southeastern United States

How do we know so much, yet know so little?
Lyme Disease

- Caused by *Borrelia burgdorferi*

- Vectors: *Ixodes scapularis* and *I. pacificus*
  - Also detected in other ticks
    - *A. americanum*
    - *I. affinis*

- Reservoir: *Peromyscus* spp. and other rodents, rarely other mammals
  - Found in mammals and ticks in Northeast and Southeast
  - PCR reports in lizards from SC/FL

- White-tailed deer – important as hosts to adult ticks

Clark, 2004; Clark et al., 2005
National Lyme disease risk map with four categories of risk

Established* and reported** distribution of the Lyme disease vectors Ixodes scapularis (I. dammini) and Ixodes pacificus, by county, United States. 1907-1996

Note: This map demonstrates United States. The true risk may differ from that shown in the accompanying map, which is obtained from state health departments.

*at least 6 ticks or 2 life stages (larvae, nymphs, adults) identified.
**at least 1 tick identified.
National prevalence: 5.0%

Almost 1 million dogs tested

Bowman et al., in press Vet Parasitol
Lyme in dogs

Dwight Bowman
Lyme disease and STARI in South

- Lyme or similar disease observed in patients from the South
  - *B. lonestari* detected by PCR in culture media of a tick removed from a STARI patient (James et al., 2001 J Infect Dis)
  - 30 STARI patients were negative for *B. lonestari* and *B. burgdorferi* (Wormser et al., 2005 Clin Infect Dis)
  - 9 STARI patients from MO were C6 ELISA negative (Phillip et al., 2006 Clin Vaccine Immunol)
**Borrelia lonestari**

- Detected in LST throughout the Southeast
  - Cultured from LST
- Detected by PCR in wild WTD
- WTD experimentally susceptible to *B. lonestari*
  - By culture inoculation
  - By wild tick exposure
- *B. lonestari* doesn’t create EM lesions in rabbits

Moore et al., 2003 J Clin Microbiol
Varela et al., 2004, J Clin Microbiol
Moyer et al., 2006 Vet Microbiol
Varela-Stokes, 2007 J Med Ent
Little et al., unpublished
Use of WTD to prove Bb transmission beyond tick-rodent cycles in Southeast

Bb evidence
- SNAP and IFA +
- SNAP + and IFA -

other Borrelia evidence?
- IFA + and SNAP -

Negative populations
- IFA and SNAP -

Murdock et al., submitted VBZD
B. burgdorferi s.s. from North and South are not genetically distinct based on *rrf-rrl* intergenic spacer (Oliver et al., in press, J Parasitol)
Other *Borrelia*

- **Borrelia lonestari**
  - *A. americanum*
  - WTD

- **Borrelia bissetti**
  - *I. scapularis, I. affinis* and *I. minor*
  - *Peromyscus gossypinus, Sigmodon hispidus,* and *Neotoma floridana*
  - Lizards from FL

- **Borrelia andersoni**
  - *Ixodes dentatus* and *I. scapularis*
  - Rabbits
  - Lizards from SC/FL

- **Borrelia carolinensis**
  - *I. minor* from South Carolina
  - *P. gossypinus* and *N. floridana* from South Carolina

- **Borrelia sp. related to *B. turicatae***
  - *Ornithodorus* soft ticks from Texas
  - Florida and Texas canines
LST-transmitted pathogen discussion points

- Determine if known organisms are human pathogens
  - i.e., *R. amblyommii*, *B. lonestari*, etc.
- Identification of other organisms that may be emerging pathogens
- Effects of modification of landscape
  - Suburbanization
  - Prescribed fire
  - Alteration of habitats that alter host dynamics
    - i.e., does the dilution hypothesis apply to LST-organisms?
LST-transmitted pathogen discussion points

- Who is more important to *E. ewingii*?
  - Dogs? Deer?

- Culture isolation of *E. ewingii* and *Ehrlichia* sp. PME

- Serodiagnostic antigens that are specific to *E. chaffeensis*, *E. ewingii*, *E. canis*, etc.

- Need for large-scale prospective studies of humans in high tick exposure areas to determine general exposures
Ixodes-transmitted pathogen discussion points

*Borrelia*:
- Greater genetic diversity in South
- Greater host range in South
- Greater number of tick vectors in South
  - Why few/no human cases?
- Zoonotic potential of various southern *Borrelia* spp.?
  - Many have been found in *I. scapularis*
Ixodes-transmitted pathogen
discussion points

- Surveys and fine scale niche modeling to determine distribution and diversity of *Borrelia* spp.

- Is *I. scapularis* transmitting *B. b.s.s.* to deer in South – if so, might it also to humans
  - Alternative vectors, such as *I. affinis* wouldn’t explain AR/LA +’s

- *Anaplasma*:
  - Similar to *Borrelia*… maybe?
General discussion points

- Increasing distribution of ticks
  - Is the density of ticks also increasing?

- Is the prevalence of pathogens increasing in tick populations?
  - If so, what is the driver

- Are tick-borne diseases still highly focal

- What is best surveillance tool for tick-borne pathogens?
  - Wildlife testing
  - Domestic animal / human testing
  - Tick surveys
    - Do all wildlife populations that have the appropriate tick vector also harbor pathogen X?

- Is there, and if so, what is causative agent of STARI ?!
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Questions and/or Discussion?

Pathogen Biology and Ecology: Tomorrow at 9am in Room 116