Introduction to Tick Borne Rickettsial Disease Surveillance in North Carolina
Spotted Fever Group Rickettsia/RMSF
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Slide 1- Title

Slide 2-

Hi my name is Carl and in this presentation will discuss Rocky Mountain Spotted Fever and Lyme disease. While we will not discuss Ehrlichia and Anaplasma specifically the principles and practices that are used for RMSF surveillance and investigation are applicable to Ehrlichia and Anaplasma

Slide 3-

RMSF is the most common vectorborne disease reported in NC. Additionally it can be fatal if not treated promptly with antibiotics. As such it is important to understand the basic ecology of the disease, the key requirements for surveillance, and the prevention messages for the general public and health care providers. While this presentation is far from exhaustive, it does provide a basic foundation. Several recent peer reviewed references are available which can provide you with more detailed information.

Slide 4-

In general all ticks have a basic life cycle which includes the egg, larvae, nymph and adult. Ticks must take a blood meal to develop from larvae to nymph and from nymph to adult. Ticks may feed on a variety of species including mammals and reptiles. Dermacentor ticks, which transmit RMSF, typically feed on mammals and it is during this period of feeding that the pathogen is transmitted. Dogs as well as people may acquire RMSF from ticks.

Slide 5-

Ticks do not drop on to people from trees. Rather, they exhibit a behavior called questing whereby they wait patiently sensing their local environment for changes in chemicals such as CO2 that would indicate a suitable mammalian host is near. Once identified the tick attaches to the mammal, attaches and begins to take a blood meal.

Slide 6-

From NCSU Extension service: http://www.ces.ncsu.edu/depts/ent/notes/Urban/ticks.htm

The adult American dog tick, Dermacentor variabilis, is active in the spring, summer, and fall. It lives along woodland paths, in recreational parks, farm pastures, wastelands, and other shrubby habitats in rural and suburban areas of North Carolina. In each stage of its life cycle, this tick may feed on a different animal. For example, the larvae feed only on white-footed field mice and meadow voles or pine voles, whereas nymphs prefer medium-sized mammals such as opossum or raccoons. Adults prefer humans and dogs as hosts. In North Carolina and throughout the southeastern United States, the American dog tick is the vector of Rocky Mountain spotted fever. However, this species does not transmit Lyme disease. The American dog tick is found throughout North Carolina, but it is most common in the Piedmont area.

- Pathogen is maintained in wild by a lifecycle of transmission between ticks and small mammals
- Ticks are the natural hosts and serve as both reservoirs and vectors for R. rickettsii
- Humans are only accidental and dead end hosts
- D. variabilis is the tick vector
- R. rickettsii persists through trans-stadial and trans-ovarial transmission in the tick vector
- Overwintering larvae can acquire RMSF transovarially (mother to egg) yielding RMSF-infected larvae

Slide 7-

Rocky Mountain spotted fever is a serious illness with a 23% mortality rate if untreated. Mortality in the US is currently less than 5%, with fatal cases often resulting from delayed initiation of antimicrobial therapy because the characteristic rash may be absent early in the course of disease. There is also increasing awareness that other, likely less pathogenic spotted fever rickettsioses may be responsible for human illness frequently confused with Rocky Mountain spotted fever, including disease associated with the tickborne pathogen Rickettsia parkeri or other Rickettsia species.

Here we see images due to infection with R. parkeri which does generally cause an eschar at the site of tick attachment. Infection with R. ricketsii does not cause eschar formation.

Slide 8-

In addition to the identification of other rickettsial pathogens that may cause illness similar to, but likely less severe than, RMSF it is known that the classic RMSF serologic tests are genus rather than species specific. As a result elevated titers to "R. ricketsii" may in fact be elevated due to infection with R. rickettsii, R. parkeri, R. amblyommii, or other rickettsial species. As a result the case definition was changed from RMSF to Spotted Fever Group Rickettsia in 2010 to more accurately reflect what serologic tests were identifying.

Slide 9-

Although RMSF cases have been reported throughout most of the contiguous United States, five states (North Carolina, Oklahoma, Arkansas, Tennessee, and Missouri) account for over 60% of RMSF cases. The primary tick that transmits R. rickettsii in these states is the American dog tick (Dermacentor variabilis Dermacentor andersoni).

In eastern Arizona, RMSF cases have recently been identified in an area where the disease had not been previously seen. Between 2003 and 2010, roughly 140 cases had been reported, and approximately 10% of the people diagnosed with the disease in this part of the state have died. The tick responsible for transmission of R. rickettii in Arizona is the brown dog tick (Rhipicephalus sanguineus), which is found on dogs and around people's homes. Almost all of the cases occurred within communities with a large number of free-roaming dogs.

Slide 10-

Anywhere from 300-600 cases are reported annually in NC. In NC there is a strong summertime seasonality associated with SFR.

People will begin to become infected in March and cases will begin to appear in your workflows shortly thereafter. This graph represents confirmed and probable cases together. In NC about 95% of all cases of SFR are probable only and are based on a single elevated IgG serologic titer. This is consistent with national data. As we will discuss later collection of a convalescent serum sample would be ideal as it would allow confirmation of many cases. However, it is difficult to convince HCWs to collect a convalescent sample once the patient has been treated and responds appropriately.

Health of the patient is paramount, and treatment is critical. However, if you can arrange to obtain a convalescent sample that would be ideal.

Slide 11-

Why Conduct Surveillance?
Ongoing surveillance is necessary to monitor the geographic and temporal occurrence of disease to so that clinicians can maintain a high awareness of the disease and the public kept adequately informed about their risk of contracting the disease

Slide 12-

This is the classic clinical triad of illness for RMSF. It is essential to educate providers in your community to treat patients with suspected RMSF infection promptly. Waiting for a classic clinical picture to develop can be fatal.

For surveillance purposes a fever along with one of the listed symptoms is required to fulfill the case definition requirements. However, if a clinician suspects infection with a Rickettsia species they should be encouraged to treat the patient appropriately and quickly even in the absence of some symptoms.

Slide 13-

From the CDC website, this is a picture of a child with a rash due to RMSF. While most people with RMSF (90%) have some type of rash during the course of illness, some people do not develop the rash until late in the disease process, after treatment should have already begun. Approximately 10% of RMSF patients never develop a rash. It is important for physicians to consider RMSF if other signs and symptoms support a diagnosis, even if a rash is not present.

A classic case of RMSF involves a rash that first appears 2-5 days after the onset of fever as small, flat, pink, non-itchy spots (macules) on the wrists, forearms, and ankles and spreads to include the trunk and sometimes the palms and soles. Often the rash varies from this description and people who fail to develop a rash, or develop an atypical rash, are at increased risk of being misdiagnosed.

The red to purple, spotted (petechial) rash of RMSF is usually not seen until the sixth day or later after onset of symptoms and occurs in 35-60% of patients with the infection. This is a sign of progression to severe disease, and every attempt should be made to begin treatment before petechiae develop.

When transmitted to a human host, pathogenic R rickettsii localize and multiply in endothelial cells of small to medium-sized blood vessels, causing a vasculitis. This vasculitis is the underlying mechanism for most of the clinical features and laboratory abnormalities of RMSF.

Widespread rickettsial-induced vasculitis leads to small areas of microhemorrhage, increased vascular permeability, edema, and activation of the humoral inflammatory and coagulation mechanisms. Leakage of fluid from the bloodstream into tissues can have devastating results when critical organs such as the lung or brain are involved, because both sites lack lymphatic vessels to remove interstitial fluid.

Slide 14-

Serologic testing is the most practical and specific method to confirm RMSF. Of the available serologic tests, indirect fluorescent antibody (IFA) testing is the most widely available and best method. The sensitivity of IFA testing is poor in the first 10 to 12 days of symptoms. Sensitivity increases to 94% when a convalescence serum sample from days 14 to 21 is used [3, 68]. However, early treatment may blunt or abolish the appearance of antibodies in the convalescent phase of illness. The IFA also cannot distinguish infections between members of the spotted fever group of rickettsiae.

Ideally an acute specimen should be collected at the time of illness onset (or presentation to HCW), treatment initiated, and a convalescent specimen collected two to three weeks later. Because treatment should be based on clinical signs the acute specimen may be held until the convalescent sample is collected. Then they can be submitted together for evaluation.

Slide 15-

This slide serves as a reminder that one should never wait for laboratory diagnostics in the event a patient has a clinically compatible illness. In the event RMSF or illness due to SFR is suspected, treatment should be initiated promptly.

Adults: Doxycycline 100mg BID

Children: Doxycycline 2.2mg/kg BID

Patients should be treated for at least 3 days after the fever subsides and until there is evidence of clinical improvement. Standard duration of treatment is 7-14 days

Pregnant: tetracyclines generally contraindicated, but might be warranted in life-threatening situations where clinical suspicion of RMSF is high.

In cases of life threatening allergies to doxycycline and in some pregnant patients for whom the clinical course of RMSF appears mild, chloramphenicol may be considered as an alternative antibiotic. Oral formulations of chloramphenicol are not available in the United States, and use of this drug carries the potential for other adverse risks, such as aplastic anemia and Grey baby syndrome. Furthermore, the risk for fatal outcome is elevated in patients who are treated with chloramphenicol compared to those treated with doxycycline. Other antibiotics, including broad spectrum antibiotics are not effective against R. rickettsii, and the use of sulfa drugs may worsen infection.

Slide 16-

Case definition

Case Definition Clinical Criteria: Any reported fever and one or more of the following: rash, eschar, headache, myalgia, anemia, thrombocytopenia, or any hepatic transaminase elevation.

No Fever no case

<u>Lyme Disease</u>

Slide 17-

This section of the presentation will focus on Lyme disease. While this is the most common vectorborne disease in the US, it has a much lower incidence rate in NC. Nonetheless a great deal of attention is often focused on Lyme disease and it has a relatively complex surveillance algorithm. It is hoped that this presentation will help you as you conduct surveillance for Lyme disease.

Slide 18-

Lyme disease Learning Objectives:

- Describe the basic ecology of LD
- Know the surveillance case definition
- Describe the case classification process
- Characterize the degree to which under-reporting occurs

Slide 19-

What is Lyme Disease?

- The most common vector borne disease in the US
- Tick borne illness due to infection with Borrelia burgdorferi sensu stricto and is transmitted by the bite of an infective Ixodes scapularis tick.

It is important to know that not all ticks serve as a vector for LD, only I. scapularis serves as a vector. I. scapularis is often incorrectly referred to as the deer tick, however the correct common name for the tick is the black legged tick.

Slide 20-

Larvae and nymphs of Ixodes scapularis, the black-legged tick, feed on lizards and small mammals. The nymphs and adults attack small and larger mammals including dogs and deer. Adults are active in late fall, in early spring, and in winter when temperatures rise above freezing. The black-legged tick is found in the same habitats and regions of North Carolina as the lone star tick.

Slide 21-

A competent reservoir host for the agent of Lyme disease readily acquires infection from vector ticks, permits spirochetes to proliferate, and readily infects vector ticks. In white-footed mice, infection generally becomes established after a single feeding by an infectious tick, and more than half retain infection for approximately 6 months. As many as three-quarters of the larval ticks that feed on such mice acquire infection.

(Donahue et. al. Reservoir competence of white-footed mice for Lyme disease spirochetes. Am J Trop Med Hyg 1987; 36:92-6.)

White tailed deer are the preferred hosts of adult I. scapularis. They are poor reservoirs for B. burgdorferi and serve chiefly to maintain the population of ticks.

Slide 22-

This slide shows confirmed and probable cases of LD by year of onset from 2000 to 2012. Since the probable case classification became available in 2008 most cases have been classified as probable. As we will discuss, probable cases are not based on objective clinical criteria as probable cases are, only a subjective determination that an illness is due to infection with Bb ss and laboratory evidence supportive of infection.

Slide 23-

The graph displays the number of reported cases of Lyme disease from 2003 through 2012. The number of confirmed cases ranged from a low of 19,804 in 2004 to high of 29,959 in 2009.

In contrast to NC, you can see that most cases are confirmed.

In 2012, 95% of Lyme disease cases were reported from 13 states:

Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey,

New York, Pennsylvania, Vermont, Virginia, Wisconsin

Lyme disease is the most commonly reported vectorborne illness in the United States – – in 2012, it was the 7th most common Nationally Notifiable disease. However this disease does not occur nationwide and is concentrated heavily in the northeast and upper Midwest.

Slide 24-

When looking at cases of LD stratified by age we see quite a difference between NC and national data. NC data do not show the classic bimodal distribution in age that is seen nationally.

Slide 25-

Why conduct Surveillance for LD?

Ongoing surveillance is needed to monitor the demographic geographic and temporal patterns of disease, identify risk factors for transmission and evaluate prevention and control strategies.

CSTE position statement 10 – ID – 06

Slide 26-

The incidence rate and risk for LD is not uniform across NC. Certain counties do have noticeably higher incidence rates as shown here.

Slide 27-

This risk map was published in 2012 and is based on the density of infected nymphal I. scapularis ticks. The high risk areas appear in red and correspond to those portions of the

country with the highest incidence rates. As you can see the NE portion of North Carolina is identified as a transitional risk area.

Slide 28-

This incidence rate map shows that there are pockets of higher incidence rates scattered across the state including the NE portion as predicted in the Diuk Wasser paper.

Slide 29-

This map overlays those counties that are designated as endemic; show with red stars. Classifying a county as endemic is based on a greater probability that at least two confirmed cases of dermatologic LD were acquired in the county. However as you can see this may have some limitations as the endemic counties do not appear to share geographic similarity with areas of higher incidence rates.

Slide 30-

As you review the case definition for Lyme disease you will note that it requires assessment of acarological risk in addition to the clinical and laboratory components to appropriately classify a case. While the data presented by Diuk wasser provides a risk assessment based on geography that is not what we use for the case definition. For case classification purposes we assess whether or not exposure may have occurred in an endemic county (as previously shown).

Slide 31-

Dermatologic additional notes: Erythema migrans (EM) is defined as a skin lesion that typically begins as a red macule or papule and expands over a period of days to weeks to form a large round lesion, often with partial central clearing.

A single primary lesion must reach greater than or equal to 5 cm in size across its largest diameter. Secondary lesions also may occur. Annular erythematous lesions occurring within several hours of a tick bite represent hypersensitivity reactions and do not qualify as EM.

MS additional notes: Recurrent, brief attacks (weeks or months) of objective joint swelling in one or a few joints, sometimes followed by chronic arthritis in one or a few joints.

Nervous system additional notes: Any of the following, alone or in combination: lymphocytic meningitis; cranial neuritis, particularly facial palsy (may be bilateral); radiculoneuropathy; or, rarely, encephalomyelitis.

CV system additional notes: Acute onset of high-grade (2nd-degree or 3rd-degree) atrioventricular conduction defects that resolve in days to weeks and are sometimes associated with myocarditis.

Slide 32-

LD Surveillance Criteria: Acarological Risk

- Known exposure is defined as having been (less than or equal to 30 days before onset of EM) in wooded, brushy, or grassy areas (i.e., potential tick habitats) in a county in which Lyme disease is endemic. A history of tick bite is not required.
- A county in which Lyme disease is endemic is one in which at least two laboratory confirmed cases have been acquired in the county or in which established populations of a known tick vector are infected with B. burgdorferi.

Wake, Guilford and Haywood are endemic

Slide 33-

LD Surveillance Criteria: Laboratory

- Positive culture for B. burgdorferi
- Positive two-tier testing interpreted using established criteria
- Positive single-tier IgG immunoblot seropositivity interpreted using established criteria.

Slide 34-

CDC currently recommends a two-step process when testing blood for evidence of antibodies against the Lyme disease bacteria. Both steps can be done using the same blood sample.

The Two-tier Testing Decision Tree describes the steps required to properly test for Lyme disease. The first required test is the Enzyme Immunoassay (EIA) or Immunofluorescence Assay (IFA). If this test yields negative results, the provider should consider an alternative diagnosis; or in cases where the patient with has had symptoms for less than or equal to 30 days, the provider may treat the patient and follow up with a convalescent serum. If the first test yields positive or equivocal results, two options are available: 1) If the patient has had symptoms for less than or equal to 30 days, an IgM Western Blot is performed; 2) if the patient has had symptoms for more than 30 days, the IgG Western Blot is performed. The IgM should not be used if the patient has been ill for more than 30 days.

The two steps of Lyme disease testing are designed to be done together. CDC does not recommend skipping the first test and just doing the Western blot. Doing so will increase the frequency of false positive results and may lead to misdiagnosis and improper treatment.

Now let's discuss the concept of a "false positive" test

Slide 35-

The illustration depicts the likelihood of false positive and false negative test results based on the prior probability of a disease occurring in a given population. Clinicians should consider the likelihood of disease before performing laboratory testing. The likelihood that a patient has a disease depends on many factors: Has a patient been in an area where the disease is found? Does the patient have signs and symptoms typical of the disease? Does the patient have risk factors for contracting or developing the disease? In populations where disease is rare or unlikely, testing is likely to lead to false positives more frequently than true positives.

As you will see based on results in NCEDSS, false positive results for LD may be common in NC.

Slide 36-

A technique designed to separate and identify antibodies that a person has produced against various antigens expressed by B. burgdorferi s.s.

Slide 37-

What is Laboratory Evidence of Infection for Surveillance?

- Two tier positive is lab evidence of infection
- IgG WB alone is lab evidence of infection
- **EIA alone is NOT**
- **IgM WB alone is NOT**

Slide 38-

PCR-based assays are being used more often in clinical settings, and they have several distinct advantages over serology. They detect the presence of infectious agents directly and can be highly sensitive. Unlike serology, they don't rely on the development of antibodies, which can take several weeks. Nevertheless, PCR testing has limitations as well. For example, DNA testing does not distinguish between living and dead organisms, and laboratory contamination with

amplified DNA poses a risk for false-positive results. This leads to the question. is PCR useful for the diagnosis of Lyme disease? In general, the answer is no.

Slide 39-

LD Case Classification

Confirmed:

1. a case of EM with a known exposure, or
2. a case of EM with laboratory evidence of infection and without a known exposure or
3. a case with at least one late manifestation with laboratory evidence of infection.

Probable: any other case of physician-diagnosed Lyme disease that has laboratory evidence of infection (non-objective manifestations)

Suspect: a) a case of EM where there is no known exposure and no laboratory evidence of infection, or b) a case with laboratory evidence of infection but no clinical information available (e.g. a laboratory report).

Slide 40-

As you can see thousands of LD events are created for investigation based on positive laboratory results, yet most events are not classified as cases of Lyme disease for surveillance purposes. This is an example of one type of false positive result.

Slide 41-

This algorithm is uses receipt of a positive laboratory report as the starting point for investigation because that is how the vast majority of LD events and cases begin. As discussed the next steps are to determine if objective clinical manifestations or known exposure occurred. This will allow you to classify the cases.

Slide 42-

What's in NCEDSS?

- Of the 4201 "events" for 2008 - 2011 there were
- 315 cases (75 confirmed & 240 probable) identified.

NOTE that only 7.5% of all LD events actually become confirmed or probable cases.

For purposes of comparison, during the same time period, approximately 25% of Rocky Mountain Spotted Fever (RMSF) events and 31% of Human Monocytic Ehrlichiosis events actually become confirmed or probable cases.

Slide 43-

Summary

- Lyme disease is frequently tested for in NC patients
- It is essential to use the appropriate testing algorithm to reduce the likelihood of false positives
- The incidence rate in NC is lower than classically endemic areas
- Cases of LD are likely very under-reported
- Areas of high incidence may be expanding