

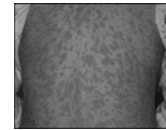
Vector-borne Infections: Rickettsia, Ehrlichia, Anaplasma, & Borrelia



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Case 1

- Immunohistochemistry on a skin biopsy reveals *Rickettsia rickettsii*



Vector-borne Infections

- Vector
 - An animal, most often an arthropod, which picks up a pathogen and transmits it to a susceptible individual.
- Reservoir
 - an ecological niche where a pathogen lives and multiplies (can serve as a source of infection)
- Host
 - An organism that is infected with or is fed upon by a parasitic or pathogenic organism

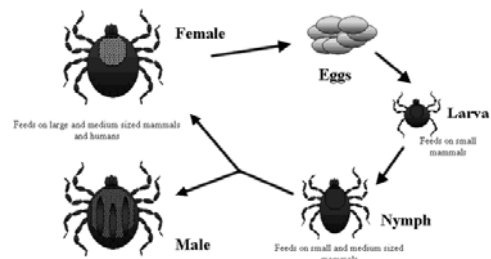
Rocky Mountain Spotted Fever (RMSF)

- Caused by *R. rickettsii*, small GN bacillus
- The most severe rickettsial disease in U.S.
- Transmitted to humans via tick bite (60% recall a bite)
- Ixodid (hard ticks) are both the reservoir and vector for RMSF
 - American dog tick or RM wood tick, depending on location
- Hosts: various mammals--depends on tick and stage of development

Case 1

- It's June in Oklahoma. A 12 YO boy develops fever and rash.
- He was bitten by a tick 10 days ago.
- Five days later he developed the sudden onset of fever, chills, severe headache, and muscle pain.
- He then developed a rash that started on his wrists and ankles and subsequently spread inward to cover his whole body.
- He presents in multi-organ system failure and dies in the emergency room before antibiotics can be administered.

Tick Lifecycle



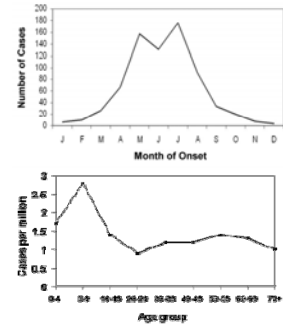
History



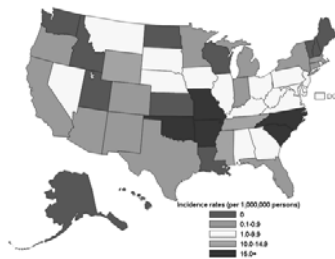
- 1896- Recognized in Snake River Valley, Idaho
- “Black measles” killed 100s
- Howard T. Ricketts discovered the causative agent
- Ricketts died of typhus (another Rickettsial disease) in Mexico in 1910

RMSF Epidemiology

- 90% of cases occur May—September
- Children are at the greatest risk (2/3 cases <15 YO)
- Exposure to dogs and residence in a wooded/high grass area may increase risk (1 exposure to vector)



“Rocky Mountain” is a Misnomer:
most common in SE/S. Central states



•Also has wide Geographic distribution in the Western hemisphere

Clinical Presentation

- After ~1 week incubation: acute onset of flu-like symptoms (i.e. fever, myalgias, severe headache, malaise, nausea/vomiting)
- 2-5 days later a macular rash appears on the wrists/ankles (rash in 90-95%)
- Rash spreads centripetally (proximally) and can become maculopapular (from edema)→petechial (from hemorrhage) w/o treatment

RMSF in NYC

Manhattan	9	4	10
Bronx	3	1	10
Total	23	7	24

Late/Severe Disease

- Full body petechial rash with palm/sole involvement
- Abdominal and joint pain
- Edema, ischemia, hypovolemia, and multi-organ system failure (from microvascular injury)
- Labs: hyponatremia, thrombocytopenia, & elevated liver enzyme levels
- Severe/fatal cases associated with: advanced age, male sex, African-American, chronic alcohol abuse, and glucose-6-phosphate dehydrogenase (G6PD) deficiency

Pathogenesis

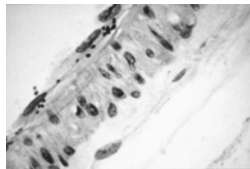
- Introduction of *R. rickettsii* at the bite site
- Travels via lymphatics to the circulation where it invades endothelial cells
 - OmpA/B mediate adherence
- The organism is engulfed, but escapes the phagosome
 - Phospholipase D and tlyC lyse the membrane
- Replication in the cytosol by binary fission

Diagnosis

- Clinical Suspicion
- Immunohistochemistry on a skin biopsy
- Serologic tests (IFA) and PCR available
 - results take time
- Culture and staining difficult and not recommended

Pathogenesis

- RickA activates host cell actin, which pushes it to the cell surface or nucleus
 - Extracellular release (to other organ systems) or
 - Cell to cell spread*
- The major pathogenic effect is increased vascular permeability resulting from the disruption of junctions between endothelial cells.
- *R. rickettsii* in endothelial cells in a blood vessel wall:

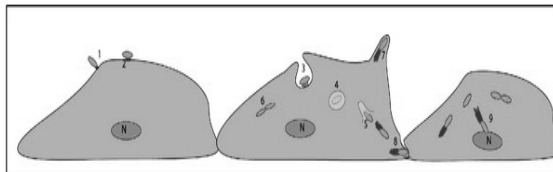


RMSF Treatment

- Doxycycline (a tetracycline)
- Use even in children
- **DO NOT DELAY TREATMENT** while awaiting laboratory confirmation
- Or else...



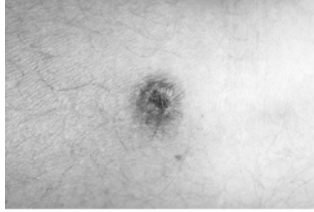
Pathogenesis



Case 2

- A Columbia medical student trying to save money finds an extra-cheap rental in the neighborhood
- She develops a little bite on her upper arm
- 10 days later she gets terrible flu-like symptoms
- A diffuse macular rash develops that becomes papulovesicular
- She thinks it's odd that she has the chickenpox again

The bite site reveals an eschar:



Source: Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL, Isselbacher KJ. *Harrison's Principles of Internal Medicine*, 16th Edition. <http://www.accessmedicine.com>. Copyright © The McGraw-Hill Companies, Inc. All rights reserved.



Her home reveals: mice!



"Every Thursday I do her nails."

Rickettsialpox

- Clinical presentation as per case
- Regional lymphadenopathy
- Diagnosis is clinical, but immunohistochemistry on a skin biopsy may be used
- Disease is self-limited w/o treatment
- Doxycycline may be used

Rickettsialpox

- Etiology: *R. akari*
- Transmitted by a mite bite
- Reservoir: mice
- Most commonly recognized in NYC

Epidemic Typhus

- *R. prowazekii*
- Vector: human body louse
- Reservoir: Humans
- Humans infected after scratching infected louse species into the bite
- Outbreaks occur in crowded, unsanitary conditions

Epidemic Typhus



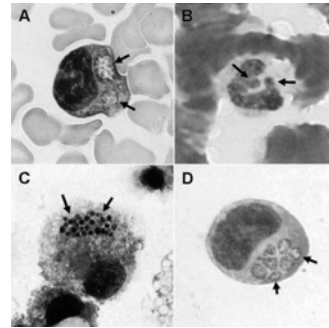
Ehrlichioses

- Tickborne infections caused by members of the Anaplasmataceae family
- *Ehrlichia chaffeensis* causes Human Monocytic Ehrlichiosis (HME)
- *Anaplasma phagocytophilum* causes Human Granulocytic Anaplasmosis (HGA)
- These are very small, obligate intracellular, Gram negative bacteria that generally have a coccoid appearance
- They target either monocytes or granulocytes and are named accordingly

Epidemic Typhus

- Serious illness, ~1 week incubation
- Fever, myalgia, severe HA, cough
- Cetrifugal rash (spreads outward), but spares the face, palms, soles
- Multiorgan system failure, fatal 5-40%
- Brill-Zinsser disease: reactivation (less severe)

Morulae, Latin for 'mulberry'

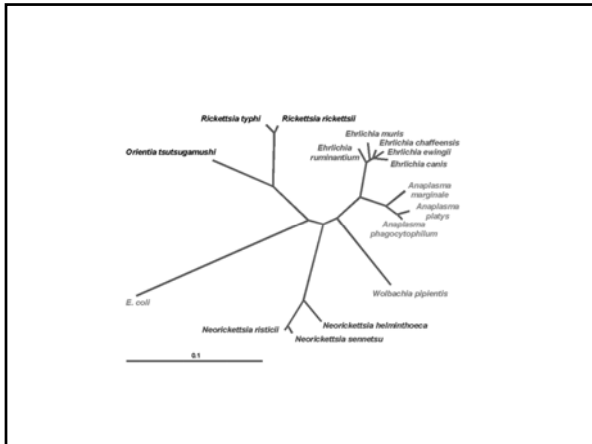


Case 3

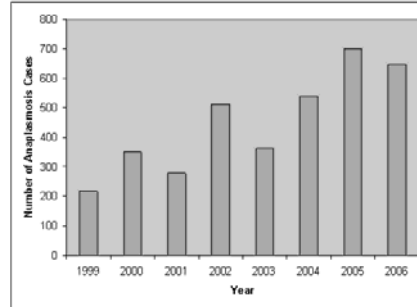
- A 65 YO avid gardener and golfer who lives in Westchester, NY presents in June with fever, myalgias, arthralgias, headache, malaise, and nausea.
- Lab tests: leukopenia, thrombocytopenia, and elevated liver enzymes
- Doxycycline is prescribed
- PCR is positive for *Anaplasma phagocytophilum* and there is a 4-fold increase in convalescent antibody titers.

A little history

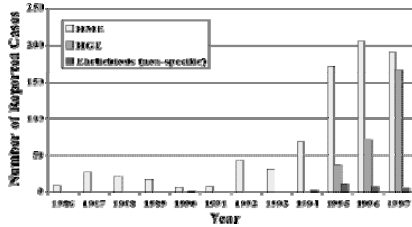
- Ehrlichioses first described by vets
- Human ehrlichiosis due to *Ehrlichia chaffeensis* was first described in 1987
- HGA: first recognized 1990
 - Wisconsin patient
 - intraneutrophilic inclusions
- 1994--causative agent (*Anaplasma phagocytophilum*) was recognized as distinct from *E. chaffeensis*



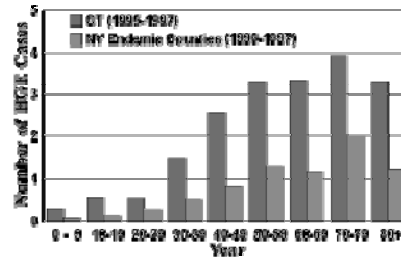
Number of Anaplasmosis cases reported to CDC by state health departments, 1999-2006.



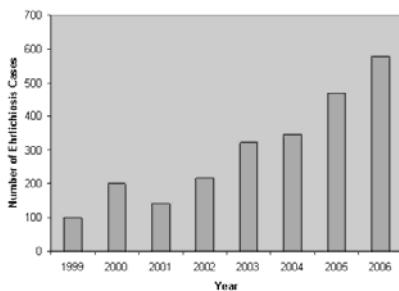
Epidemiology: An emerging pathogen (most cases—occur April to September)



Average annual reported HGE rate (per 100,000) by age group, in NY and CT, 1995-1997



Number of Ehrlichiosis cases (caused by Ehrlichia chaffeensis) reported to CDC by state health departments, 1999-2006.



HME--Epidemiology

- S. Central, SE, mid-Atlantic states
- Vector: Ixodes ticks (hard ticks)
 - Lone Star tick (*Amblyomma americanum*)
- Reservoir: white-tailed deer



HGA--Epidemiology

- NE, mid-Atlantic, Upper Midwest, Pacific NW states + internationally
- Vector: Ixodes ticks (hard ticks)
 - *I. scapularis* (aka blacklegged tick or deer tick) or Western Blacklegged tick
- Reservoir: small mammals (esp. white-footed mice)



Pathogenesis

- Still being elucidated*
- Introduced via tick bite and binds to the cell membrane of target WBC
- Internalized and form clusters inside cytoplasmic vacuoles—morulae
- Key to survival is preventing fusion of the phagosome with the lysosome

Clinical Presentation

- Can be a mild illness/asymptomatic to a severe, fatal infection (up to 3%)
- Immunocompromise (HIV, asplenic, on steroids/chemotherapy) puts at risk for more severe disease

Some specifics-- Pathogenesis HGA

- Msp-2 binds to PSGL-1 (CD162), a receptor on neutrophils/granulocytes
- Bacteria stay in early endosome and acquire nutrients for replication (type 4 secretion apparatus)
- Secretes one protein, AnkA, which binds to nuclear proteins (role unclear)
- Neutrophil function disrupted--including endothelial cell adhesion and transmigration, motility, degranulation, respiratory burst, and phagocytosis.

Clinical Presentation: similar to rickettsial diseases, but less likely to get a rash

Table 1. Meta-analysis of human monocytic ehrlichiosis (HME) and human granulocytic anaplasmosis (HGA) symptoms, signs, and laboratory findings.

Symptom, sign, or finding	Patients, % (no. evaluated)	
	HME	HGA
Symptom or sign		
Fever	97 (633)	93 (621)
Myalgia	57 (250)	77 (510)
Headache	80 (240)	76 (385)
Malaise	82 (234)	94 (288)
Nausea	64 (143)	38 (258)
Vomiting	33 (152)	26 (95)
Diarrhea	23 (107)	16 (65)
Cough	26 (155)	19 (260)
Arthralgias	41 (211)	46 (504)
Flash	31 (286)	6 (357)
Stiff neck	3 (240)	21 (24)
Confusion	19 (279)	17 (211)
Laboratory finding		
Leukopenia	62 (276)	49 (336)
Thrombocytopenia	71 (247)	71 (336)
Elevated serum AST or ALT level	83 (276)	71 (172)

NOTE. Data are from 11. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Diagnosis and Treatment

- Clinical suspicion (fever/flu symptoms) in endemic region during tick season
- PCR—acutely, diagnostic tool of choice
- Serologic—look for 4x rise in antibodies
 - Most sensitive test
- Examination of peripheral blood for morulae (very low yield)
- Treatment: Doxycycline

HME Outbreak

- 1993 Outbreak in a "Golf-oriented Retirement Community" in TN
- Wildlife reserve next door
- 11 cases
- Increased risk: tick bites, exposure to wildlife, no insect repellent, golfing, and among golfers, retrieving lost golf balls from the rough

• *NEJM* Volume 333:420-425, August 17, 1995

Case 4

- His symptoms resolved on their own, but a few months later, his knee looked like this:



Case 4

- A 23 YO man camping in Lyme, CT gets a rash that looks like this:



Lyme Disease

- Etiology: *Borrelia burgdorferi*, a Gram negative spirochete
- The most common vector-borne disease in the U.S.
- Predominant in the NE
- Vector: Ixodes tick—usually the nymph (must feed 24+ hrs)
- Reservoir: white-footed mouse for nymphal/larval ticks and white-tailed deer for adult ticks
- Peak transmission: June, July, August

Case 4

- Because he smokes a lot of marijuana, he forgets about the rash.
- After a few weeks, he looks like this:

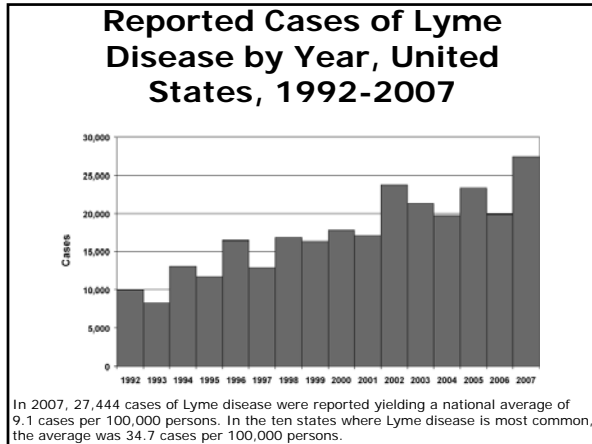


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Reported Cases of Lyme Disease -- United States, 2007

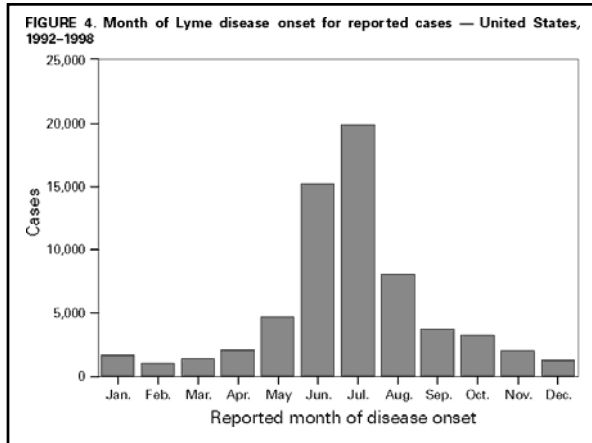


1 dot placed randomly within county of residence for each reported case



Removing the Tick per the CDC:

- Remove a tick from your skin as soon as you notice it. Use fine-tipped tweezers to firmly grasp the tick very close to your skin. With a steady motion, pull the ticks body away from your skin. Then clean your skin with soap and warm water. Throw the dead tick away with your household trash.
- Avoid crushing the ticks body. Do not be alarmed if the ticks mouthparts remain in the skin. Once the mouthparts are removed from the rest of the tick, it can no longer transmit the Lyme disease bacteria. If you accidentally crush the tick, clean your skin with soap and warm water or alcohol.
- Don't use petroleum jelly, a hot match, nail polish, or other products to remove a tick.

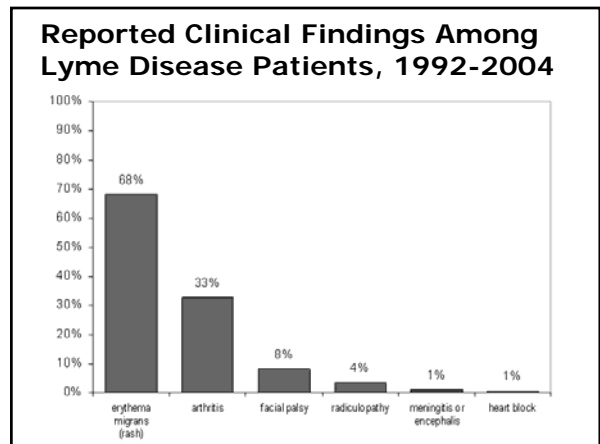


Clinical Presentation

- Local: erythema migrans
 - Early: may also have fever, flu-symptoms
- Early neurologic disease:
 - Meningitis or radiculopathy
 - Cranial nerve palsy
- Cardiac disease:
 - Heart block, myopericarditis
- Late Disease:
 - Arthritis, CNS or PNS disease

I. scapularis

- The *I. scapularis* nymphal ticks that spread *B. burgdorferi* are very small!



Pathogenesis

- *B. burgdorferi* inoculated into the skin at the bite site, multiplies, and spreads outward causing the characteristic rash
- OspC variant helps determine dissemination
- Facilitating hematogenous spread:
 - OspA binds plasminogen
 - Surface proteins binding platelet-specific integrin
- DbpA & DbpB mediate binding to decorin, a peptidoglycan on the surface of collagen
 - Binding to collagen matrix in ECM of joints, heart, C/PNS
- Other surface proteins bind:
 - Heparan & dermatan sulfate (endo/epithelial cells)
 - Fibronectin (an extracellular matrix protein)
- Host Immune Response

History Continued

- 1949- First treated with penicillin
- 1970- First case of EM in the US
- 1975- Outbreak of what first appeared to be juvenile rheumatoid arthritis in 3 SE CT towns including Lyme and Old Lyme
 - Health Dept first contacted by 2 mothers -- Polly Morray & Judith Mensch
- 1982- Spirochete cultured from Shelter Island ticks

Diagnosis

- If there is erythema migrans, diagnosis can be clinical
- Acute/convalescent antibodies
- CSF examination may be indicated
 - Lymphocytosis, elevated protein, normal glucose
- Co-infection with HGA and babesia may occur (same vector!)


Treatment Essentials

- Doxycycline (or alternative) for erythema migrans
- Oral regimen may also be used for isolated Bell's palsy, mild cardiac disease, arthritis
- IV Ceftriaxone (3rd gen cephalosporin) for heart block, symptomatic cardiac disease, other PNS/CNS disease

History

- 1883- Skin manifestations identified by Buchwald in Breslau, Germany
- 1909- Arvid Afzelius, a Swedish dermatologist, coined the term 'erythema migrans'
- 1920s- neuro symptoms identified
- 1930s- connection made between EM and neuro symptoms
- 1940s- illness associated w/spirochetes

Table 2. Recommended antimicrobial regimens for treatment of patients with Lyme disease.

Drug	Dosage for adults	Dosage for children
Preferred oral regimens		
Amoxicillin	500 mg 3 times per day ^a	50 mg/kg per day in 3 divided doses (maximum, 500 mg per dose) ^a
Doxycycline 	100 mg twice per day ^a	Not recommended for children aged <8 years For children aged ≥8 years, 4 mg/kg per day in 2 divided doses (maximum, 100 mg per dose)
Cefuroxime axetil	500 mg twice per day	30 mg/kg per day in 2 divided doses (maximum, 500 mg per dose)
Alternative oral regimens		
Selected macrolides ^b	For recommended dosing regimens, see footnote d in table 3	For recommended dosing regimens, see footnote d in table 3
Preferred parenteral regimen		
Ceftriaxone	2 g intravenously once per day	50–75 mg/kg intravenously per day in a single dose (maximum, 2 g)
Alternative parenteral regimens		
Cefotaxime	2 g intravenously every 8 h ^c	150–200 mg/kg per day intravenously in 3–4 divided doses (maximum, 6 g per day) ^c
Penicillin G	18–24 million U per day intravenously, divided every 4 h ^c	200,000–400,000 U/kg per day divided every 4 h ^c (not to exceed 18–24 million U per day)
^a Although a higher dosage given twice per day might be equally as effective, in view of the absence of data on efficacy, twice-daily administration is not recommended. ^b Tetracyclines are relatively contraindicated in pregnant or lactating women and in children <8 years of age. ^c Because of their lower efficacy, macrolides are reserved for patients who are unable to take or who are intolerant of tetracyclines, penicillins, and cephalosporins. ^d Dosage should be adjusted for patients with impaired renal function.		

Indication	Treatment	Duration, days (range)
Tick bite in the United States	Doxycycline, 200 mg in a single dose ^{1,2} ; 4 mg/kg in children ≥ 8 years of age ¹ and/or observation	...
Erythema migrans	Oral regimen ^{3,4}	14 (14-21)
Early neurologic disease	Oral regimen ^{3,4}	14 (14-21)
Meningitis or radiculopathy	Parenteral regimen ^{5,6}	14 (10-28)
Cranial nerve palsy ^{7,8}	Oral regimen ^{3,4}	14 (14-21)
Cardiac disease	Oral regimen ^{3,4,9} or parenteral regimen ^{5,6}	14 (14-21)
Borrelial lymphocytoma	Oral regimen ^{3,4}	14 (14-21)
Acute disease	Oral regimen ³	28
Arthritis without neurologic disease	Oral regimen ^{3,4}	28
Recurrent arthritis after oral regimen	Oral regimen ^{3,4} or parenteral regimen ^{5,6}	14 (14-28)
Antibiotic-refractory arthritis ¹⁰	Symptomatic therapy ¹¹	...
Central or peripheral nervous system disease	Parenteral regimen ^{5,6}	14 (14-28)
Acanthamoebiasis chronica atrophicans	Oral regimen ³	21 (14-28)
Post-Lyme disease syndrome	Consider and evaluate other potential causes of symptoms; if none is found, then administer symptomatic therapy ¹²	...

NOTE: Regardless of the clinical manifestation of Lyme disease, complete response to treatment may be delayed beyond the treatment duration. Relapse may occur with any of these regimens; patients with objective signs of relapse may need a second course of treatment.

¹ See text.

² A single dose of doxycycline may be offered to adult patients and to children ≥ 8 years of age when all of the following circumstances exist: (1) the exposed tick can be reliably identified as an adult or nymphal Ixodes scapularis tick that is estimated to have been attached for ≥ 36 h on the basis of degree of engorgement of the tick with blood or of certainty about the time of exposure to the tick; (2) prophylaxis can be started within 72 h after the time the tick was removed; (3) ecologic information indicates that the local rate of infection of these ticks with *Borrelia burgdorferi* is $\geq 20\%$, and (4) doxycycline is not contraindicated. For patients who do not fulfill these criteria, observation is recommended.

³ See table 2.

⁴ For adult patients intolerant of amoxicillin, doxycycline, and cefuroxime axetil, azithromycin (500 mg orally per day for 7-10 days), clarithromycin (500 mg orally twice per day for 14-21 days, if the patient is not pregnant), or erythromycin (500 mg orally 4 times per day for 14-21 days) may be given. The recommended dosages of these agents for children are as follows: azithromycin, 10 mg/kg per day (maximum of 500 mg per day); clarithromycin, 7.5 mg/kg twice per day (maximum of 500 mg per dose); and erythromycin, 12.5 mg/kg 4 times per day (maximum of 500 mg per dose). Patients treated with macrolides should be closely observed to ensure resolution of the clinical manifestations.

⁵ Ten days of therapy is effective if doxycycline is used; the efficacy of 10-day regimens with the other first-line agents is unknown.

⁶ For nonpregnant adult patients intolerant of β -lactam agents, doxycycline (200-400 mg/day orally or intravenously, if the patient is unable to take oral medication) in 2 divided doses may be adequate. For children ≥ 8 years of age, the dosage of doxycycline for this indication is 4-8 mg/kg per day in 2 divided doses (maximum daily dosage of 200-400 mg).

⁷ See text. Patients without clinical evidence of meningitis may be treated with an oral regimen. Parenteral antibiotic therapy is recommended for patients with both clinical and laboratory evidence of aseptic meningitis. Most of the experience in the use of oral antibiotic therapy is for patients with severe facial nerve palsy. Whether oral therapy would be as effective for patients with other cranial neuropathies is unknown. The decision between oral and parenteral antibiotic therapy for patients with other cranial neuropathies should be individualized.

⁸ A parenteral antibiotic regimen is recommended at the start of therapy for patients who have been hospitalized for cardiac monitoring; an oral regimen may be substituted to complete a course of therapy or to treat ambulatory patients. A temporary pacemaker may be required for patients with advanced heart block.

¹⁰ Antibiotic-refractory Lyme arthritis is operationally defined as persistent synovitis for at least 2 months after completion of a course of intravenous ceftriaxone or after completion of two 4-week courses of an oral antibiotic regimen for patients who are unable to tolerate ceftriaxone; in addition, PCR of synovial fluid specimens and synovial tissue specimens, if available, is negative for *B. burgdorferi* nucleic acids.

¹¹ Symptomatic therapy might consist of nonsteroidal anti-inflammatory agents, intra-articular injections of corticosteroids, or other medications; exact evaluation with a rheumatologist is recommended. If persistent synovitis is associated with significant pain or if it limits function, arthroscopic synovectomy may be considered.

Common Themes in this Lecture

- Exposure to vector-reservoir
 - Time of year
 - Geographic location
 - Possible history of bite
- Clinical presentation often involves a flu-like illness and possibly a rash
- Doxycycline is often the treatment of choice!

Case #5

- Time: May 2009
- Place: Sag Harbor, Long Island
- Who: Lilly, my 2-year old
- What happened: My husband found a tick on her, but it was not attached
- What I did: Nothing
- Until 5 days later...

Prevention is the best medicine!
Prevent exposure to the vector! Use bug repellent, protective clothing, and do tick checks!



Amoxicillin was prescribed