

COURSE: Medical Microbiology, MBIM 650/720 - Fall 2009

TOPIC Rickettsia, Orientia, Ehrlichia, Anaplasma, Coxiella and Bartonella

Lecture 55

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TEACHING OBJECTIVES:

1. To describe the interactions of the *Rickettsia*, *Orientia*, *Ehrlichia*, *Coxiella*, and *Bartonella* with the host cell.
2. To describe the pathogenesis, epidemiology, and clinical syndromes associated with *Rickettsia*, *Ehrlichia*, *Coxiella*, and *Bartonella*.
3. To discuss the methods for treatment, prevention, and control of these diseases.

Suggested Reading:

Murray *et al.* Medical Microbiology, 6th Ed., Chapters 44 and 45, and pages 371-373 (Chapter 38).

KEY WORDS:

Rickettsia, *Orientia*, *Ehrlichia*, *Anaplasma*, *Coxiella*, *Bartonella*, reservoir, vector, Rocky Mountain spotted fever, Ehrlichiosis, Rickettsialpox, Scrub typhus, Epidemic typhus, Murine typhus, Q fever, Trench fever, Cat-scratch disease, transovarian passage, Weil-Felix test, Brill-Zinsser disease, morula

RICKETTSIA, ORIENTIA, EHRLICHIA, ANAPLASMA, COXIELLA

Rickettsial infections have played a significant role in the history of Western civilization. Epidemic typhus has been known since the 16th century and it has long been associated with famine and war. The outcome of several wars was influenced by epidemic typhus. Typhus killed or caused great suffering in over 100,000 people in the two World Wars. In spite of its long history, it was not until the early part of the 20th century that the causative agent was determined. Howard Ricketts described the causative agent of Rocky Mountain spotted fever and was able to culture it in laboratory animals. Others then realized that the causative agent of epidemic typhus was related to the organism that Ricketts described. After the discovery of the importance of arthropod vector in the spread of typhus, vector control measures were instituted to control the disease.

The *Rickettsia*, *Orientia*, *Ehrlichia*, *Anaplasma*, and *Coxiella* are all small obligate intracellular parasites which were once thought to be part of the same family. Now, however, they are considered to be distinct unrelated bacteria. Like the *Chlamydia* these bacteria were once thought to be viruses because of their small size and intracellular life cycle. However, they are true bacteria structurally

similar to Gram negative bacteria. These bacteria are small Gram negative coccobacilli that are normally stained with Giemsa, since they stain poorly by the Gram stain. Although these bacteria are able to make all the metabolites necessary for growth, they have an ATP transport system that allows them to use host ATP. Thus, they are energy parasites as long as ATP is available from the host.

All of these organisms are maintained in animal and arthropod reservoirs and, with the exception of *Coxiella*, are transmitted by arthropod vectors (e.g., ticks, mites, lice, or fleas). Humans are accidentally infected with these organisms. The reservoirs, vectors and major diseases caused by these organisms are summarized in Table 1.

Table 1. Diseases caused by and vectors of <i>Rickettsia</i>, <i>Orientia</i>, <i>Ehrlichia</i>, <i>Anaplasma</i>, and <i>Coxiella</i>			
Disease	Organism	Vector	Reservoir
Rocky Mountain spotted fever	<i>R. rickettsii</i>	Tick	Ticks, wild rodents
Ehrlichiosis	<i>E. chaffeensis</i> <i>E. erwingii</i> <i>A. phagocytophilum</i>	Tick	Deer Deer Small mammals
Rickettsialpox	<i>R. akari</i>	Mite	Mites, wild rodents
Scrub typhus	<i>O. tsutsugamushi</i>	Mite	Mites, wild rodents
Epidemic typhus	<i>R. prowazekii</i>	Louse	Humans, squirrel fleas, flying squirrels
Murine typhus	<i>R. typhi</i>	Flea	Wild rodents
Q fever	<i>C. burnetii</i>	None	Cattle, sheep, goats, cats

I. *Rickettsia* and *Orientia* (*Orientia* were formerly classified in *Rickettsia*)

- A. Replication (Figure 1; Source: Baron, Medical Microbiology, 4th Ed., Fig. 38-4) - The *Rickettsia* preferentially infect endothelial cells lining the small blood vessels by parasite-induced phagocytosis. Once in the host cell the bacteria lyse the phagosome membrane with a phospholipase and get into the cytoplasm where they replicate. Mode of exit from the host cell varies depending upon the species. *R. prowazekii* exits by cell lysis while *R. rickettsii* get extruded from the cell through local projections (filopodia). F actin in the host cell associates with *R. rickettsii* and the actin helps to “push” the bacteria through the filopodia. *O. tsutsugamushi* exits by budding through the cell membrane and remains enveloped in the host cell membrane as it infects other cells.

B. Antigenic structure -
Based on their antigenic composition the

Rickettsia are divided

into several groups. The organisms in each group, the diseases caused by the organisms and their geographical distribution are summarized in Table 2 (Source: Murray, *et al.*, Medical Microbiology 3rd Ed. Table 43-1).

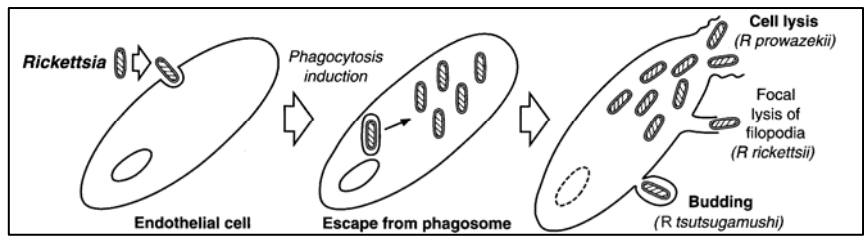


Figure 1. Replication cycle of *Rickettsia* and *Orientia*

Table 2. Diseases caused by <i>Rickettsia</i>.		
Organism	Disease	Distribution
Spotted fever group		
<i>R. rickettsii</i>	Rocky Mountain spotted fever	Western hemisphere
<i>R. akari</i>	Rickettsialpox	USA, former Soviet Union
<i>R. conorii</i>	Boutonneuse fever	Mediterranean countries, Africa, India, Southwest Asia
<i>R. sibirica</i>	Siberian tick typhus	Siberia, Mongolia, northern China
<i>R. australis</i>	Australian tick typhus	Australia
<i>R. japonica</i>	Oriental spotted fever	Japan
Typhus group		
<i>R. prowazekii</i>	Epidemic typhus Recrudescent typhus Sporadic typhus	South America and Africa Worldwide United States
<i>R. typhi</i>	Murine typhus	Worldwide

Scrub typhus group		
<i>O. tsutsugamushi</i>	Scrub typhus	Asia, northern Australia, Pacific Islands

C. Pathogenesis and Immunity - Pathogenesis is primarily due to destruction of the cells by the replicating bacteria. Destruction of the endothelial cells results in leakage of blood and subsequent organ and tissue damage due to loss of blood into the tissue spaces. No evidence for immunopathological damage has been obtained. Both humoral and cell mediated immunity are important in recovery from infection. Antibody-opsonized Rickettsia are phagocytosed and killed by macrophages and delayed type hypersensitivity develops following rickettsial infections.

D. *R. rickettsii* (Rocky Mountain spotted fever)

1. Epidemiology - Rocky Mountain spotted fever is the most common rickettsial disease in the United States with 400-700 cases occurring annually. While the disease was originally described in the Rocky Mountain states, it is now most common in the South Central states, including South Carolina (Figure 2; Source: Murray, *et al.*, Medical Microbiology 3rd Ed. Fig. 43-5). The organism is transmitted by the bite of an infected tick with most infections occurring from April through September. The rickettsia in the tick are in a dormant state and must be activated by the warm blood meal and released into the saliva of the tick. Thus, prolonged exposure (24 - 48 hrs) to an infected tick must occur before the organisms can infect the human host. The principal reservoir for *R. rickettsii* is the ixodid (hard) tick where transovarian passage occurs. Wild rodents can become infected and act as a reservoir for the bacteria but this is not considered to be the main reservoir.

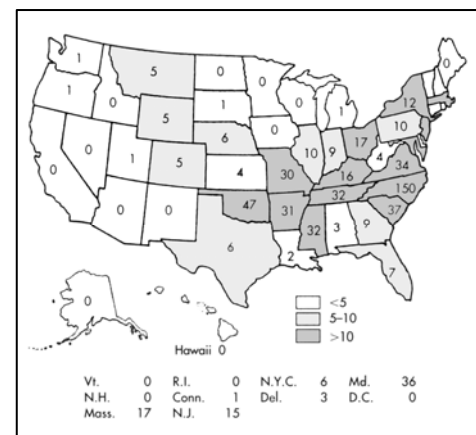


Figure 2. Distribution of Rocky Mountain Spotted Fever

2. Clinical syndromes - Rocky Mountain spotted fever begins with the abrupt onset of fever, chills, headache, and myalgia, usually 2-12 days after the tick bite. Patients may not recall being bitten by a tick. Rash usually (90% of cases) appears 2-3 days later. The rash begins on the hands and feet and spreads centripetally towards the trunk. Rash on the palms and soles is common. Initially the rash is maculopapular but in the latter stages may become petechial and hemorrhagic (Figure 3; Source: Murray, *et al.*,

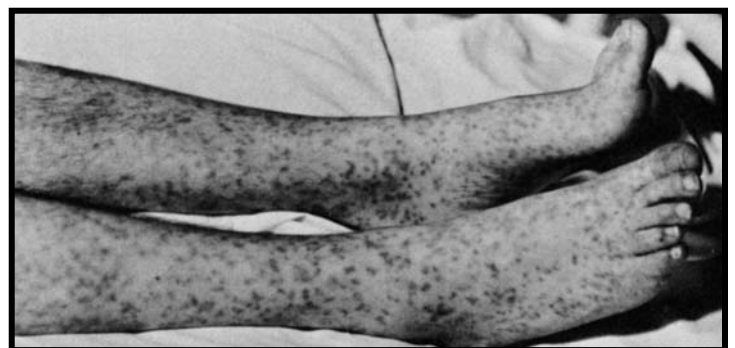


Figure 3. Rash of Rocky Mountain Spotted Fever

Medical Microbiology 3rd Ed. Fig. 43-6). Complications from widespread vasculitis can include gastrointestinal symptoms, respiratory failure, seizures, coma and acute renal failure. Complications occur most frequently in cases in which the rash does not develop, since treatment is usually delayed. Mortality rate in untreated patients is 20%.

3. Laboratory diagnosis - Initial diagnosis should be made on clinical grounds and treatment should not be delayed until laboratory confirmation is obtained. A fluorescent antibody test to detect antigen in skin punch biopsies is the fastest way to confirm a diagnosis. However this test is available only in reference laboratories. PCR based methods are also available but limited to reference laboratories. The Weil-Felix test, which is an agglutination test to detect antibodies that cross react with *Proteus vulgaris*, is no longer recommended. The primary laboratory diagnostic tool is serology. Indirect fluorescent antibody tests and latex agglutination tests are available for serological diagnosis of Rocky Mountain spotted fever.
4. Treatment, prevention and control - *R. rickettsii* is susceptible to tetracyclines and chloramphenicol. Prompt treatment is necessary since morbidity and mortality increases if treatment is delayed. No vaccine is available. Prevention of tick bites (protective clothing, insect repellents, etc.) and prompt removal of ticks are the best preventative measures. It is not feasible to attempt to control the tick reservoir.

E. *R. akari* (rickettsialpox)

1. Epidemiology - *R. akari* is found in the United States and sporadic infection occurs. The vector is a mouse mite and the reservoirs are mites and mice. In mites the bacteria are maintained by transovarian transmission. Humans are accidentally infected.
2. Clinical syndromes - Rickettsialpox is typically a mild disease that has two phases. In the first phase a papule develops at the site of the mite bite and quickly ulcerates and forms an eschar. This initial phase occurs approximately 1 week after the bite. After an incubation time of 7-24 days the second phase of the disease occurs. This phase is characterized by sudden onset of fever, chills, headache and myalgia and is followed 2 to 3 days later with a generalized rash. The rash is papulovesicular and crust over in the later stages. The pox heal within 2 to 3 weeks without scarring. Fatalities are rare.
3. Laboratory diagnosis - Not available except in certain reference laboratories
4. Treatment and prevention and control - Tetracyclines can speed up recovery. Measures aimed at controlling mouse populations help to prevent the disease.

F. *R. prowazekii* (Epidemic typhus or louse-borne typhus)

1. Epidemiology - Epidemic typhus is a disease transmitted by the human body louse. When an infected louse bites a human it defecates and the bacteria are found in the feces. Irritation caused by the bite causes the person to scratch the bite and thereby to inoculate the bacteria into abraded skin. Unlike the other rickettsial diseases, humans are the primary reservoir for *R. prowazekii*. Epidemic typhus occurs among people living in crowded, unsanitary,

conditions such as those found during wars, famine, and natural disasters. Transovarian transmission in the louse does not occur since lice die several weeks after being infected. The disease occurs sporadically in the United States, primarily in the Eastern states where the reservoirs are flying squirrels and their fleas. The flea is the vector that transmits the disease.

2. Clinical syndromes

- a. Epidemic typhus is characterized by sudden onset of fever, chills, headache, myalgia, and arthralgia, after an average incubation period of 8 days. Approximately 7 days later a rash develops in most patients. The rash is maculopapular but can be petechial or hemorrhagic. In contrast to the rash seen with Rocky Mountain spotted fever, the rash in epidemic typhus develops on the trunk first and spreads to the extremities (centrifugal spread). Complications include: myocarditis, stupor, and delirium. The name typhus comes from the Greek for “smoke” underscoring the fact that stupor and delirium often complicate the disease. Recovery may take several months. The mortality rate varies but can be quite high (60-70%) in some epidemics.
- b. Brill-Zinsser disease is recrudescent epidemic typhus. It occurs decades after the initial infection. In the United States it is most commonly seen in those who were exposed to epidemic typhus in World War II. The clinical course of the disease is similar to epidemic typhus but is milder and recovery is faster. The skin rash is rarely seen. Diagnosis is made on the basis of a fever with unknown origin and a history of previous exposure to epidemic typhus.

3. Laboratory diagnosis - Diagnosis should be made on clinical findings and treatment should begin before laboratory confirmation. Weil-Felix antibodies are produced but the test is not recommended. Serology is the primary laboratory test used for diagnosis of *R. prowazekii*. Indirect fluorescent antibody tests and latex agglutination tests are available. Patients with epidemic typhus initially have an IgM response followed by IgG antibodies whereas patients with Brill-Zinsser disease initially have an anamnestic IgG response. Isolation of the organism is possible but dangerous.

4. Treatment, prevention and control - Tetracyclines are highly effective. Louse control measures can prevent infection. A killed typhus vaccine is available and is recommended for use in high-risk populations.

G. *R. typhi* (Murine or endemic typhus)

1. Epidemiology - Murine typhus occurs worldwide with approximately 40-60 cases being reported in the United States annually. Rats are the primary reservoir for the disease which is transmitted by the rat flea vector. The normal cycle is rat to flea to rat and humans are accidentally infected. Since there is no transovarian transfer in the flea, the flea is not a reservoir for the disease. The cat flea can also be a vector for the disease in the United States. The bacteria are in the flea feces and are inoculated into abraded skin by scratching the area irritated by the bite.
2. Clinical syndromes - The symptoms of fever, chills, headache, and myalgia appear abruptly 1-2 weeks after infection. A rash develops in many but not all cases. The rash begins on the trunk and spreads to the extremities, unlike the rash seen in Rocky Mountain spotted fever. The disease is mild and resolves within 3 weeks even if untreated.
3. Laboratory diagnosis - A serological indirect fluorescent antibody test is used to detect antibodies to *R. typhi*.
4. Treatment, prevention and control - Tetracyclines are effective. Controlling the rodent reservoir is useful in preventing infection. A vaccine is not available.

H. *Ortientia tsutsugamushi* (Scrub typhus)

1. Epidemiology - Scrub typhus occurs in Asia, Australia and the Pacific Islands. The disease is transmitted to humans by chiggers, the larval form of a mite. The mite is both the reservoir and the vector and the transmission is transovarial. Rodents can also act as a reservoir. The normal cycle is mite to rodent to mite; humans are accidentally infected.
2. Clinical syndromes - The disease is characterized by sudden onset of fever, chills headache and myalgia 1-3 weeks after contracting the bacteria. A maculopapular rash develops 2-3 days later. The rash appears first on the trunk and spreads to the extremities (centrifugal spread). Mortality rate in outbreaks are variable .
3. Laboratory diagnosis - Serological tests for antibody are available.
4. Treatment, prevention and control - Tetracyclines (doxycycline) are effective. Avoiding exposure to chiggers will prevent the disease.

II. Ehrlichia and Anaplasma

- A. Replication - (Figure 4; Source: Baron, Medical Microbiology, 4th Ed. Fig. 38-4). The *Ehrlichia* and *Anaplasma* preferentially infect leukocytes. They enter the cell by phagocytosis and once in the host cell they inhibit phagolysosome fusion. The organisms grow within the membrane bound phagosome and are released by lysis of the cell. The inclusion body containing the organisms is called a morula.

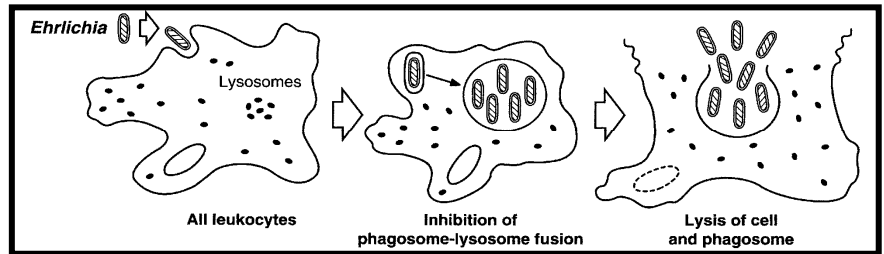


Figure 4. Replication cycle of Ehrlichia

- B. Epidemiology - Table 3 (Source: Murray, *et al.*, Medical Microbiology 5th Ed. Table 46-1) summarizes the human diseases caused by the *Ehrlichia* and *Anaplasma*, the vectors, reservoirs, and the geographic distributions.

Table 3. Diseases caused by and vector of <i>Ehrlichia</i> and <i>Anaplasma</i>.				
Organism	Disease	Vector	Reservoir	Distribution
<i>E. chaffeensis</i>	Human monocytic ehrlichiosis	Lone Star tick	White-tailed deer	Southeastern, Mid-Atlantic and South Central United States
<i>E. ewingii</i>	Primarily dog disease Human granulocytic ehrlichiosis	Lone Star tick	White-tailed deer	Southeastern, Mid-Atlantic and South Central United States
<i>A. phagocytophilum</i>	Human granulocytic ehrlichiosis	Deer and dog ticks	Small mammals	Wisconsin, Minnesota, Connecticut

- C. *E. chaffeensis* (human monocytic ehrlichiosis)

1. Clinical syndromes - The disease resembles Rocky Mountain spotted fever except that the rash does not develop in most (80%) patients. In addition leukopenia, thrombocytopenia, and elevated serum transaminases are observed in the majority of patients. Mortality is low (<5%).
2. Laboratory diagnosis - Microscopic observation of morula in blood smears is rare and although culture is possible it is rarely attempted. Serological test are available and are the most commonly employed test. DNA probes are available and may replace serological test.

3. Treatment, prevention and control - Patients should be treated with doxycycline. Avoidance of tick infected areas and protective measures (clothing and insect repellents) can prevent the disease.

D. *E. ewingii* and *Anaplasma phagocytophilum* (human granulocytic ehrlichiosis)

1. Clinical syndromes - The disease is similar to human monocytic ehrlichiosis.

2. Laboratory diagnosis - Same as *E. chaffeensis*

3. Treatment, prevention and control - Same as *E. chaffeensis*

III. *Coxiella burnetii* (Q fever; [Q for query])

A. Replication - (Figure 5; Source: Baron, Medical Microbiology, 4th Ed. Fig. 38-4) *C. burnetii* infects macrophages and survives in the phagolysosome where they multiply. The bacteria are released by lysis of the cells and phagolysosomes.

B. Pathogenesis and immunity - Infection occurs by inhalation of airborne particles. The organism multiplies in the lungs and is disseminated to other organs. Pneumonia and granulomatous hepatitis are

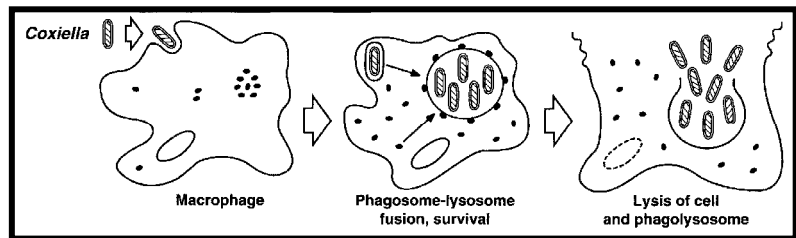


Figure 5. Replication cycle of *C. burnetii*

observed in patients with severe infections. Phase variation occurs in the LPS of *C. burnetii*. In acute disease, antibodies are produced against the phase II antigen. In chronically infected patients antibodies to both phase I and phase II antigens are observed. Cellular immunity is important in recovery from the disease.

C. Epidemiology - *C. burnetii* is extremely stable in the environment and has “spore-like” characteristics. *C. burnetii* infects a wide range of animals including goats sheep cattle and cats. The organism is found in the placenta and in the feces of infected livestock. The organisms persist in contaminated soil and is a focus for infection. *C. burnetii* is also passed in milk and people who consume non-pasteurized milk can become infected. There is no arthropod vector for *C. burnetii*. *C. burnetii* is found worldwide and infection is common in ranchers, veterinarians, abattoir workers, and others associated with cattle and livestock.

D. Clinical syndromes - The disease can be mild and asymptomatic and is often undiagnosed. The disease can be acute or chronic. In acute Q fever the patient presents with headache fever, chills, and myalgia. Respiratory symptoms are usually mild (“atypical pneumonia”). Hepatomegaly and splenomegaly may be observed. Granulomas can be seen in histological section of most patients with Q fever. Chronic Q fever typically presents as endocarditis generally on a damaged heart valve. Prognosis of chronic Q fever is not good.

- E. Laboratory diagnosis - Serology is most commonly used to diagnose Q fever. Antibodies to phase II antigen is used to diagnose acute disease and antibodies to both phase I and phase II antigens to diagnose chronic disease.
- F. Treatment, prevention and control - Tetracycline is used to treat acute Q fever. Chronic disease is treated by a combination of antibiotics. A vaccine is available but is not used in the United States.

IV. *Bartonella*

- A. Microbiology - The *Bartonella* are small, Gram-negative, aerobic bacilli that are difficult to grow in culture. They are found in many different animals but they cause no apparent disease in animals. Insects are thought to be vectors in human disease. Some species are able to infect erythrocytes while others simply attach to host cells. Table 4 (Source: Murray, *et al.*, Medical Microbiology 3rd Ed. Table 35-3) summarizes the organisms and the diseases they cause.

Table 4. Diseases caused by <i>Bartonella</i>.	
Organism	Disease
<i>B. quintana</i> (formerly <i>Rochalimaea quintana</i>)	Trench fever (shin-bone fever, 5 day fever), bacillary angiomatosis, bacillary peliosis endocarditis
<i>B. henselae</i>	Cat-scratch disease, bacillary angiomatosis, bacillary peliosis endocarditis
<i>B. bacilliformis</i>	Oroya fever (bartonellosis, Carrion's disease)
<i>B. elizabethae</i>	Endocarditis (rare)

B. *B. quintana* (Trench fever)

1. Epidemiology - Trench fever is a disease associated with war. The vector is the human body louse and there is no known reservoir except man. Transovarian transmission in the louse does not occur. The organism is found in the feces of the louse and is inoculated into humans by scratching. The cycle is human to louse to human.
2. Clinical syndromes - Infection with *B. quintana* can result in asymptomatic to severe debilitating illness. Symptoms include fever, chills, headache, and severe pain in the tibia. A maculopapular rash may or may not appear on the trunk. The symptoms may reappear at 5 day intervals and thus the disease is also called 5 day fever. Mortality rates are very low.
3. Laboratory diagnosis - Serological tests are available but only in reference laboratories. PCR based tests have been developed.
4. Treatment, prevention and control - Various antibiotics (erythromycin, doxycycline) have been used to treat trench fever. Measures to control the body louse are the best form of prevention.

C. *B. henselae* - (Cat-scratch disease)

1. Epidemiology - Cat-scratch disease is acquired after exposure to cats (scratches, bites, and possibly cat fleas).
2. Clinical syndromes - The disease is usually benign, characterized by chronic regional lymphadenopathy.
3. Laboratory diagnosis - Serological tests are available
4. Treatment – The treatment of cat-scratch disease is controversial but azithromycin appears to be the drug of choice if treated.