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Chronic Lyme Disease Complex and Its Commonly Undiagnosed Primary and Secondary Co-Infections

Aaron Smith, John Oertle, Dan Warren, Dino Prato

Envita, Scottsdale, AZ, USA
Email: Aaron@envita.com, JohnO@envita.com, DanW@envita.com, DinoPrato@envita.com

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Abstract

Chronic Lyme disease complex describes the burden carried by patients infected with *Borrelia burgdorferi* as well as other co-infections or secondary co-infections (opportunistic infections). These infections can cause a significant burden on patients more so than Lyme disease alone. Along with the many underdiagnosed cases of Lyme disease throughout the world exists numerous undiagnosed co-infection and secondary co-infections leading to debilitating symptoms for many patients. The potential for co-infections varies by location as well as to the exposure to various species of ticks. Since there is potential for patients to experience several tick bites including those of different species, additional microorganisms also commonly transmitted via tick bite are included that are typically left out of the conversation of potential *Borrelia burgdorferi* co-infections. The most common co-infections of Lyme disease include anaplasmosis, babasiosis, bartonellosis and ehrlichiosis. Secondary co-infections or opportunistic infections commonly seen in patients with Lyme disease are also discussed. By helping to establish a comprehensive list of infections associated with Chronic Lyme disease complex may in fact help patients receive a proper diagnosis in order to administer the much needed comprehensive treatments patients deserve.

Keywords

Lyme, Anaplasmosis, Babasiosis, Bartonellosis, Ehrlichiosis, Co-Infections, Opportunistic Infection

1. Introduction

Lyme disease is caused by an infection of the spirochete *Borrelia burgdorferi* and is transmitted via Ixode tick bite. Transmission of other infections that are also commonly associated with tick bites has the potential to cause co-occurring infections with Lyme disease which if untreated can lead to what we call Chronic Lyme disease

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complex. Other opportunistic infections can become more pronounced during the stages of a chronic Lyme infection. Co-infections and opportunistic infections have the potential to complicate the treatment of chronic Lyme disease thus leading to more rigorous treatment regimens and potentially longer duration of illness. Although certain co-infections are more likely to occur via prevalence in ticks in certain geographical areas, it is important to recognize that chronic Lyme disease complex is common among those infected with Borrelia and therefore should be considered when treating chronic Lyme disease patients. Other diseases harbored by ticks that are not known to carry Lyme disease are included as potential co-infections since there is potential for multiple tick bites. Although the likelihood of some of these tick-borne infections to co-occur with Lyme disease is low, it is important to recognize all of the potential for co-infections as well as raise awareness of other possible tick infections.

2. Co-Infections Associated with Lyme Disease Complex

The following tick borne infections are not listed in order of prevalence of co-occurring with Lyme disease but instead are listed in alphabetical order. These tick infections range in severity and treatability and can be exacerbated by the immunocompromised state of individuals suffering from chronic Lyme disease complex. Research conducted on each of these co-infecting microorganisms varies in size and scope with Powassan virus being the least studied as well as the least common infection.

2.1. Anaplasmosis

Human granulocytotropic anaplasmosis (HGA) caused by *Anaplasma phagocytophilum* is spread by tick vector particularly in the eastern and midwestern regions of the United States. Cross sectional analysis shows a seroprevalence as high as 14.9% in Wisconsin [1].

The most common manifestation of symptoms include nonspecific fever, myalgia, chills, and headache [2]-[6]. Other complications can include toxic shock-like syndrome, invasive opportunistic infections of fungal and viral infections, respiratory insufficiencies, pancarditis, hemorrhage, neurologic diseases including demyelinating polyneuropathy and brachial plexopathy, acute renal failure, and rhabdomyolysis [7]-[10]. Asymptomatic presentation is possible while other infections can be fatal with an increase severity associated with a patient's age and comorbid illness [11]. The severity of HGA varies with almost half of patients requiring hospitalization and 17% of patients requiring admission to an intensive care unit [5]. Common incubation period before the presentation of symptoms is between one to two weeks.

Blood smear examination and PCR analysis during infection or serologic testing in late stage infections are the primary means of diagnosis of HGA. Blood samples should be taken prior to antibiotic treatment since the antibiotics can rapidly reduce the detectable quantities of both infected cells and bacterial DNA. Indirect fluorescent antibody method is the primary means of detecting *Anaplasma phagocytophilum* in serological testing.

The traditional agent of choice to treat *Anaplasma phagocytophilum* is doxycycline as compared with other tretracycline derivatives. Tretracyline has demonstrated usefulness *in vitro* for both Ehrlichia and Anaplasma [12]-[14]. In the absence of contraindication to tetracycline drugs, patients should be treated with intravenous (IV) or oral tetracycline. The recommended regimen for adults is 100 mg orally twice a day with clinical improvements expressed within one or two days of treatment [15]-[20]. Patients that do not respond within this time frame should be reevaluated for either alternative treatment or diagnosis.

2.2. Babesisa

Babesiosis is caused by an infection of either Babesiadivergens or Babesia microti via a tick-borne vector. They are the only protozoan tick-borne vector in the United States. The majority of the cases of babesiosis occur in the northeastern United States.

Influenza like symptoms are common one week after inoculation of either Babesiadivergens or Babesia microti. Other symptoms that might occur are fever, myalgias, sweating, and headache. High fever, hemoglobinuria, renal failure, jaundice, and hemolytic anemia makes babesiosis resemble falciparum malaria. There is also a chance that the disease can persist asymptomatically in younger adults.

Detection of protozoa in the blood stream is the primary means of diagnosing babesiosis. Other available testing includes polymerase chain reaction (PCR) and serological tests. Appropriate exposure history, fever, and hemolytic anemia is an indicator of babesiosis.

For those experiencing mild symptoms, a symptomatic approach might be the best course of treatment. 650 mg of Quinine (Quinamm) given three times a day orally for seven days in addition to 600 mg of clindamycin (Cleocin) three times a day for seven to ten days should be administered to patients with more pronounced symptoms. 750 mg of atovaquone (Mepron) given twice per day for seven to ten days with 600 mg of azithromycin (Zithromax) orally once per day for seven to 10 days is another method of treating babesiosis. It is important to note that reduced dosing is necessary for children. Severely ill patients with high parasitemia have undergone exchange transfusion.

2.3. Bartonella

Bartonella infections are more commonly known as cat-scratch disease (CSD). The infection is caused by ticks and has been reported in all areas of the continental United States but occurs more often in northern states. August through October are when the disease incidence increases and is primarily found in humid and warm locations.

Although adults can contract CSD, children are more likely to contract the disease. Lymphadenopathy is common in 85% - 90% of patients with CSD [21]. At the site of inoculation, a primary skin lesion will begin to appear with few patients not exhibiting this symptom. Lymph nodes swelling is common with the infection and patients may also experience tender lymph nodes which may eventually suppurate [22]. Patients are 75% likely to develop aching, anorexia, and malaise with only 9% experiencing a low grade fever [22]. Myalgia, arthritis, and arthralgia are common musculoskeletal problems that occur in 10% of patients.

Lymph node biopsies are necessary for patients with failing lymph nodes and whose diagnosis is uncertain. Stellate granulomas and lymphoid hyperplasia are seen in patients with CSD. Bacterial stains using silver and the morphology of *B. henselae*, which is a small, curved, and aerobic gram-negative bacteria, is necessary for its identification. With those confirmed to have CSD, it is important for doctors to follow up who have unilateral lymphadenopathy [22].

A study evaluating CSD in 1200 patients with lymphadenopathy showed that antibiotics were rarely used on patients [23]. The most common form of treatment involves the use of azithromycin (Zithromax) prescribed in dosages of 500 mg on the first day and 250 mg for the next four days in patients with CSD. 30 days after treatment with azithromycin showed that 57% of patients experienced 80% resolution at day 30 as compared to placebo where only 6.7% of patients experienced that level of remission [24]. Ciproflaxacin (Cipro), rifampin, gentamicibin, and trimethoprim/sulfamethozazole (Bactim, Septra) have been used to treat CSD [25].

2.4. Colorado Tick Fever

Coltivirus is an RNA orbivirus transmitted by a tick that causes Colorado tick fever. In the Rocky Mountain region, approximately 200 to 300 cases are reported each year. Colorado tick fever often goes unnoticed due to its benign presentation and therefore goes undetected which suggests the annual incidence could be much higher [26]. Increased risk of severe complications occurs in the immunocompromised and those that have undergone a splenectomy.

Seven days after inoculation, influenza-like symptoms begin. It is rare to have respiratory issues after contracting Colorado tick fever even though nearly one third of patients get a sore throat [2]. Rash, conjunctivitis, and meningitis are the most significant biphasic symptoms with fever. Seven to ten days is the typical duration of the disease.

Immunofluorescence following a blood smear is the most common way to diagnose Colorado tick fever. Leukopenia and thrombocytopenia are other laboratory abnormalities associated with the disease. Presentation of symptoms and exposure to ticks should be an indicator of whether the patient is likely to have Colorado tick fever.

There is no specific medication indicated to treat Colorado tick fever. However, supportive treatment should be used. Tetracycline, doxycycline, and chloramphenicol are often prescribed to treat other potential tick-borne illnesses that the patient may have been exposed to.

2.5. Ehrlichia

Ehrlichiosis is contracted via tick borne vector. There are two common subtypes of ehrlichiosis in the United States that include human granulocytic ehrlichiosis (HGE) from *Anaplasma phagocytophilum* and human monocytic ehrlichiosis (HME) caused by *Ehrlichia chaffeensis*. These two subtypes are epidemiologically distinct but are clinically indistinguishable [27]. Southeastern and southcentral United States are more likely to expe-

rience HME and typically affect adults. Northern and upper Midwestern United States is where the majority of HGE cases occur, particularly in adults that live in tick infested areas or in rural areas.

Flu like symptoms including fever, headache, myalgia, malaise, and chills. Other symptoms include petechial, macular, amulopapular rash in the upper extremities and the trunk with rarer occurrences in the palms and soles. These symptoms occur seven days after a tick bite. Although HME and HGE present similar signs and symptoms, the occurrence of a rash is remote for those infected with HGE. Differentiation between Rocky Mountain spotted fever and ehrlichiosis is difficult.

Elevated serum transaminase, leukopenia, and thrombocytopenia is evident in laboratory findings of patients with HME or HGE. Empirical treatment of patients experiencing nonspecific influenza like symptoms including fever, headache, myalgia, malaise, and chills in addition to leukopenia and thrombocytopenia should occur immediately. Seroconversion during convalescence is the principal method of diagnosing human ehrlichiosis. Serum antibody titers that are considered to be greater have values either equal to or greater than 1:128 or antibody titers with a minimum peak of 1:64 associated with a four-fold rise or fall in antibody titers.

Treatment with antibiotics should occur immediately after a diagnosis of ehrlichiosis. In adults, a dosage of 100 mg twice per day of Docycline is recommended. An alternative treatment may include 500 mg of tetracycline orally four times per day. Aplastic anemia is a risk of using chloramphenicol as an alternative to also prevent tooth decay. Although severe cases may require a longer treatment course, treatment should last for a minimum of five to seven days and should continue three days after fever subsides.

2.6. Mycoplasma

Mycoplasma pneumoniae does not have national reporting or a surveillance system. The true size of the health problem is unknown but is estimated to be approximately 2 million cases of mycoplasma pneumoniae each year in the United States.

Although pneumonia only occurs in 3% - 10% of cases of mycoplasma pneumoniae infections, mycoplasma pneumoniae is the most important form of atypical pneumonia respectively [28]. Banal bronchitis [28], earaches, rhinitis, pharyngitis, and sinusitis [29] occur most often in infections with mycoplasma pneumoniae. Other less common symptoms include maculopapular exanthema, vesicular dermatitis, encephalitis, meningitis, myelitis, cranial neuropathy, and cerebellar ataxia. Hepatitis, pancreatitis, and arthritis have also been reported from those infected with mycoplasma pneumoniae.

Several weeks after the disease becomes positive, mycoplasma pneumoniae can be detected by serology which indicates the significance of seroconversion in the chronic disease course. Although difficult and allowing low sensitivity, detection of Mycoplasma pneumoniae by PCR or cell culture is possible but not a part of the traditional diagnostic criteria.

500 mg of azithromycin, 500 mg of levofloxacin, or 400 mg doxycycline once a day for two weeks or more is the recommended treatment for mycoplasma pneumoniae.

2.7. Powassan Virus

Powassan virus is a Flavidridae virus that infects the nervous system. Flavidridae viruses are RNA viruses whose family is comprised of three genera including Flavivirus, Pestivirus, and Hepacivirus. Although the first documented case of Powassan virus occurred in the town of Powassan in Canada, Powassan has been reported in California, Connecticut, Maine, Massachusetts, New York, South Dakota, Vermont, West Virginia, and Wisconsin [11] [30]-[35]. The virus is transmitted via tick vector and infections usually occur during the summer and fall months.

Neuroinvasive syndromes, including encephalitis, meningitis, and myelitis, are the most common clinical presentation of the Powassan virus infection. Other nonspecific symptoms including fever, sore throat, somnolence, myalgia, head ache, dizziness, nausea, vomiting, lethargy, and malaise. The incubation period for Powassan virus is between 7 to 34 days [36]-[42].

Diagnosis of a Powassan viral infection can be difficult. In the majority of cases, analysis of cerebrospinal fluid (CSF) indicates a lymphocytic pleocytosis of less than 500/mm^3. Generalized slow wave activity in patients with encephalitis can be revealed by electroencephalography of patients infected by Powassan virus. In three cases, isolation of Powassan virus from postmortem brain tissue was successfully recovered. There are no commercially available diagnostic method available for the detection of Powassan virus.

Treatment of Powassan infections are supportive since there is no specific antiviral therapy available. In most

patients, anticonvulsant therapies have been enacted as well as the use of mechanical ventilation. Since Powassan virus can only be transmitted via tick bite, prevention is mostly centered around measures to avoid exposure to ticks.

2.8. Q Fever

The most common mode of *Cociella burnetii* is not through a tick but from exposure to infected cattle, particularly during birth. Western and plains states have a higher incidence of Q Fever than in other parts of the United States. Areas with a large amount of cattle ranching, sheep, and goat also have higher incidence rates for other states. Alaska and Hawaii have not had an incident of Q Fever. However, California, Colorado, Illinois, Kentucky, Missouri, Tennessee, and Texas account for over half of all human Q fever incidences. Although incidences of Q fever can happen throughout the year, the most common months of people acquiring with Q fever are during the spring and early summer months; peaking in April and May.

More than half of all people who contract Q fever do not experience any symptoms. However, symptoms including severe fever, headache, chills, and fatigue are common for acute infections. Another major clinical manifestation is atypical pneumonia. Some patients experience hepatitis as a result of an infection of *Cociella burnetii*. Myocarditis, pericarditis, skin rash, and meningoencephalitis are rare but can occur if infected.

Diagnosis of Q fever using immunohistology is the most common method. These techniques can include ELISA/ELIFA or immunofluorescence. Detection of *Cociella burnetii* must take place two to three weeks after contracting the disease. Culturing *Cociella burnetii* is a far less common method of detection due to the danger and risk of transmission to laboratory workers in addition to the lack of sensitivity using this technique.

Doxycycline and tetracycline are recommended for treatment of Q fever since the use of other antibiotics puts patients at a higher risk of severe illness. Of these two treatments, doxycycline is the most powerful and is the recommended mode of treating Q fever. Adults should take 100 mg twice a day for three days after the fever subsides. Children should take 2.2 mg/kg per body weight of doxycycline with similar duration as in adults. The typical duration period is between two to three weeks.

2.9. Relapsing Tick Fever

A spirochete in the genus Borrelia is responsible for relapsing tick fever. The bacteria is transmitted via tick bite. Exposure to rabbits, rats, mice, squirrels, and chipmunks that harbor the tick associated with relapsing tick fever, particularly west of the Mississippi river in the more mountainous regions, are likely the source of relapsing tick fever. Small or sporadic clusters of the disease occur in this region.

One week after a tick bite is the average incubation period. Symptoms include dizziness, nausea vomiting, arthralgias, and influenza like symptoms. High fevers, which are fevers greater than 40˚C (104˚F), tend to be irregular and sporadic and may also be coupled with delirium. Splenomegaly is common for most patients with relapsing tick fever. Hemoptysis, iridocyclitis, cranial nerve palsy, myocarditis, rupture of spleen, epistaxis, coma, and pneumonitis are complications that can occur.

Blood, cerebral spinal fluid, or bone marrow during a febrile episode are the easiest way to detect the spirochete. Elevations in leukocyte count and thrombocytopenia are other laboratory findings that indicate the diagnosis of relapsing tick fever.

100 mg of doxycycline twice per day for ten days is the treatment of choice. 500 mg of erythromycin four times a day for ten days is an alternative means of treating relapsing tick fever [43]. If given during the late febrile stage in particular, Jarisch-Herxheimer reaction can occur. A means to reduce this reaction can involve the use of acetaminophen two hours before the administration of antibiotics.

2.10. Rocky Mountain Spotted Fever

Rocky Mountain spotted fever is the most common rickettsial disease in the United States [44]. It is caused by an infection called *Rickettsia rickettsi* and occurs in every state in the US with the exception of Maine, Hawaii, and Alaska. Although infections can occur year round, particularly in southern states, the disease is most common in Atlantic states during the months between April and September [45]. Transmission through tick is the primary vector and there is no evidence to support that it can be transmitted from person to person. Children between five and nine years old have the highest incidence of contracting Rocky Mountain spotted fever [46].

Those that are infected by Rocky Mountain spotted fever recall a tick bite in 50% - 70% of patients [47] [48].

Five to seven days after inoculation of *Rickettsia rickettsi* is when patients begin to feel the symptoms of Rocky Mountain spotted fever. Malaise, myalgias, nausea, vomiting, headache, and fever are the most common symptoms of Rocky Mountain spotted fever. Sore throat, pleuritic chest pain, non-productive cough, and abdominal pain are also experienced by infected patients. There is also potential for neurologic compromise in addition to circulatory and respiratory failure in patients [47]. High risk patients are those who have glucose-6-phosphated-hydrogenase (G6PD) deficiencies and often lead to poor outcomes and complications [48]. The appearance of lesions on the wrist, ankles, soles, palms, and forearms are macular, pink, and often fade when pressure is applied to them. After time, the rash then becomes maculopapular and later petechial and begins to appear on the buttocks, neck, face, trunk, and axilla [49]. Ecchymosis and ulcerations may appear as the lesions begin to coalesce.

Clinical signs and symptoms are the primary means of diagnosing Rocky Mountain spotted fever. Although skin biopsies and immuneflorescence is highly specific, the sensitivity is approximately 60%. Bocytopenia and hyponatremia laboratory testing has limited usefulness [50]. During the convalescence period, latex agglutination titers and enzyme-linked immunosorbent assay (ELISA) can also be used for diagnostic purposes.

Early treatment during the course of the illness is important to obtain optimal effects and treatment should begin immediately when clinical and epidemiologic findings support the suspicion of Rocky Mountain spotted fever. A minimum of seven days treatment of chloramphenicol (Chloromycetin), tetracycline, and doxycycline (Vibramycin) can be used to treat *Rickettsia rickettsi* infections [51]. Evidence is lacking for the use of fluoroquinolones to treat Rocky Mountain spotted fever.

2.11. Tularemia

Tularemia, also known as rabbit fever, is caused by a bacteria known as *Francisella tularensis*. Southcentral, south eastern, and western United States are areas endemic of the tick vector associated with tularemia. Inoculation, contamination, inhalation, and ingestion of the bacteria is the most common form of transmission. Hunters who have skinned infected rabbits during the winter are the most common for transmission via microlesions. Transmission via tick vector is most common in the summer time but it should be noted that the disease can also spread through deer flies and horse flies. Infections can also be caused by contaminated water or consumption of infected meat even though these modes of transmission are rare.

Ulceroglandualr, oropharyngeal/gastrointestinal tract, ocularglandular, pulmonary, and typhoid tularemia are the clinical manifestations that are divided into syndromes [50]. Fever, malaise, fatigue, headache, myalgias, and headache occur rapidly after three to five days after inoculation with cough occurring in nearly one third of patients. Skin ulcers, pneumonia, nausea, vomiting, pericarditis, acute respiratory distress syndrome and sore throat are other symptoms that can occur. With the exception of glandular or typhoidal tularemia, inflammation of papules appear at the infected site. Ulcer craters with colorless exudate are seen when the papules become pustular and begin to ulcerate. Children are more likely to experience cervical or posterior auricular node infections. Femoral and inguinal nodes in adults are more likely to be affected.

Exposure to ticks, wild rodents, and rabbits with primary pustular lesion on an extremity should indicate tularemia. Although dangerous since the animal is likely to be infected, isolation of the organism from sputum, lymph nodes, or skin lesions can be used as a diagnostic tool. Culture media and infected tissue should be handled with extreme caution and doctors should be aware that the disease is considered a potential biological weapon. The diagnosis can also be confirmed by acute and convalescent titers. Although white blood cell count may be normal, leukocytosis is common. Tularemia can be differentiated from other tick-borne diseases by examining chest radiographs to see abnormal findings which include pleural effusions, hilar adenopathey, and a triad of oval opacities.

Before confirmation of laboratory tests, treatment should begin if tularemia is suspected. 0.5 g of streptomycin should be administered intermuscularly until the patient's fever is reduced to normal body temperature. Streptomycin should be used for five days after the fever subsides. Intravenous or intramuscular administration of gentamicin in three divided doses for seven to 14 days is another effective treatment option [52]. Gentamicin should be reduced if renal disease is present. The potential for relapse and prevention of node suppuration may occur if tetracyclines or chloramphenicol is used.

3. Secondary Co-Infections or Common Opportunistic Infections

Often asymptomatic infections can become symptomatic following an infection of *Borrelia burgdorferi* or ex-

acerbated by the co-infections associated with chronic Lyme disease complex. In addition to weakening of the patient's immune system from the long exposure to tick borne infections, patient will commonly present several secondary co-infections. Treatment of these opportunistic infections are necessary but may also be a burden on patients already seeking treatment. The following list cannot be exhausted since there are too many potential secondary co-infections that can be listed in a single article. However, the following infections are observed more frequently in patients with Lyme disease complex.

3.1. Candida Albicans

Candida albicans has a 16 MB genome consisting of eight pairs of chromosomal homologs that range in size from approximately 0.95 to 3.3 MB and has a high level of genome plasticity in addition to its ability to lose heterozygosity. Candida albicans is one of two Candida species that can form true hyphae and has the capability of growing as either a yeast or filamentous form. It is a dimorphic species whose hyphae is integral in both adhesion and tissue invasion.

Candidiasis has three primary characteristics which include thrush, yeast infection, and invasive candidiasis. Thrush describes a Candida infection of the mouth and throat with the most common manifestation as oral thrush which is characterized by plaques on the tongue. Other symptoms associated with thrush include angular cheilitis, difficulty swallowing, and redness or soreness in affected areas including oral mucous membranes. Symptoms of a yeast infections include the hallmark abnormal vaginal discharge which can range from a thick, white, and clumpy cottage cheese like secretion or a slightly watery white discharge. The vagina and labia can become itchy with a burning sensation. Painful intercourse and painful urination were also common. The vulva can also become red and swollen. Invasive candidiasis often manifests itself similarly to many bacterial infections with fever and chills being the most predominant symptoms. Quite often patients prescribed antibiotics and do not improve later find that they actually have invasive candidiasis.

There are several different methods of diagnosing Candida albicans. The most predominant means of diagnosis remains blood culture (BC) which has a sensitivity between 30% and 50% and requires long incubation periods [53]. Patients undergoing fluconazole prophylaxis or have deep-seated candidiasis often have negative results using blood culture as a diagnostic criteria [54] [55]. The detection of mannan antigen on the cell wall of Candida albicans can be utilized by either a latex agglutination test and ELISA with specificity of 90% - 100% for both tests [56] [57]. The sensitivity for ELISA is better with its sensitivity ranging between 30% - 60%. Detection of Candida albicans nucleic acid using PCR is significant particularly in deep-seated candidiasis with negative BCs since the sensitivity is 88% as compared to 17% for BCs [54].

There are several available treatment options for Candida Albicans that include either creams, tablets, or vaginal suppository. 5 g of Butoconazole 2% cream can be administered for a three day period or as one 2% suppository. Clotrimazole can be given as a cream or vaginal tablet. The 1% Clotrimazole cream can be administered in 5 g for seven to fourteen days and the 10% cream can be given as a 5 g single application. 100 mg Clotrimazole tablet is given once a day for seven days or two tablets for three days. The 500 mg dose of Clotrimazole requires only one tablet. 150 mg of Econazole vaginal tablet can be administered once a day for three days. Fenticonazole comes as a 2% cream and should be administered in 5 g dosages for seven days. 2% cream of Tioconazole in 5 g dosages can be administered for three days. Terconazole can be administered as either a cream or a vaginal tablet. 5 g of 0.4% Terconazole cream can be administered for seven days while 5 g of 0.8% Terconazole cream is administered over a period of three days. An 80 mg Terconazole as a vaginal suppository is administered over a period of three days. Fluconazole is a150 mg oral tablet that can be given as a single dose. Ketoconazole comes in a 200 mg tablet that is taken twice a day for five days. 100 mg tablet Itraconazole can be given twice a day for three days.

3.2. *Chlamydia pneumoniae*

Chlamydia pneumoniae is a Gram-negative bacteria which although has the genes to make peptidoglycan, the peptidoglycan is respectively undetectable, thus the chlamydial peptidoglycan paradox. Despite the autotrophic nature of *Chlamydia pneumoniae*, *Chlamydia pneumoniae* has genes associated with catabolize glucose for the generation of ATP even though these genes are turned off [58]. Elementary body (EB) and reticular body (RB) are morphologically distinct infectious and reproductive forms with unique developmental cycles. EBS are approximately 200 - 400 μm in diameter and are taken into the cell via endocytosis post infection by a process involving electrostatic binding. EB remains in the phagosome within the host cell after endocytosis where fusion

with lysosome does not occur. Binary fission occurs after EBs differentiate to RBs. Release involving either cytolysis or by exocytosis or extrusion of the entire inclusion occurs approximately 48 hr later. The host cell remains intact during this process.

The clinical presentations of *Chlamydia pneumoniae* have significant variations and can range from mild disease to severe community acquired pneumonia (CAP). Although most patients are asymptomatic, lower and upper respiratory tract infections are common with pneumonia and bronchitis being the most common. Pharyngitis, laryngitis, and sinusitis are less common but can also occur in conjunction with a lower respiratory infection or in isolation. The incubation period of *Chlamydia pneumoniae* is approximately 21 days and is significantly longer than most other respiratory infections. Initial symptoms can include sore throat, hoarseness, or rhinitis. Myalgia and chills may also be accompanied with a fever with these symptoms subsiding in the period of days or weeks. A cough is the predominant symptom of a *Chlamydia pneumoniae* infection which can lead to a protracted biphasic course of illness symptoms. Severe symptoms have been reported for those that experience neutropenia as a result of treatment or patients with acute leukemia.

Culturing *Chlamydia pneumoniae* from an infected patient is the reference starting point for diagnosis of the infection. Nasopharyngeal swabs are used to collect samples since *Chlamydia pneumoniae* is an obligate intracellular organism and these cells must be collected from host cells that can host that environment. The samples are then cultured *in vitro*. Microimmunofluorescence (MIF) and enzyme immunoassays are the most common form of serological assays performed for the diagnosis of *Chlamydia pneumoniae*.

Tetracycline, erythromycin, doxycycline are agents used particularly for acute infections while antibiotics like ampicillin, penicillin, and sulfa drugs should not be used since *Chlamydia pneumoniae* can gain resistance to those antibiotics. 500 mg of tetracycline four times a day for two weeks, 500 mg of erythromycin four times a day for two weeks, or 100 mg of doxycycline twice a day for three weeks are the best treatments for *Chlamydia pneumoniae* infections.

3.3. Cytomegalovirus

Cytomegalovirus (CMV) is a 230 kb double-stranded DNA virus and a member of the Herpesviridae family. A tegument, an icosahedron capsid, and an outer envelope surround the CMV DNA. The nuclear and cytoplasmic membrane of the host cell are components that are used to comprise the outer envelope. Three distinct viral glycoprotein complexes found in the outer envelope include gCI, gCII, and gCIII. Although the functions of these viral glycoprotein complex families are for the most part unknown, they are thought to be involved in viral attachment since antibodies to these glycoproteins block infectivity.

CMV is a primarily asymptomatic infection. However, symptomatic CMV can occur in the immunosuppressed depending on the severity of immune suppression. Symptoms include malaise (similar to that of Epstein-Barr virus), fever, myalgia, pharyngitis or skin disease, and lymphocytiosis.

CMV cannot be diagnosed on clinical presentation alone with the exception of retinitis. The diagnosis of CMV is more complex than viral isolation from patients. This is particularly true for immunosuppressed patients. Recently, the detection and diagnosis of CMV has been enhanced by monoclonal antibody technology in particular. Viral culture has been the traditional method of the diagnosis of CMV but has a turnaround time of approximately one to three weeks. Polymerase chain reaction (PCR) and nucleic acid probe methods have a higher sensitivity than cell cultures since cell cultures have the capability of creating false negatives. Antigen detection of CMV was discovered in the late 1990s and detects CMV pp 65 in circulating leukocytes before they are washed, fixed, and stained with monoclonal fluorescein or a peroxidase conjugate.

The prodrug for ganciclovir, known as valganciclovir, is activated in the liver and gut with 60% bioavailability. Intravenous ganciclovir 5 mg/kg is clinically equivalent to 900 mg of valganciclovir taken one daily. However, 900 mg of valganciclovir has side effects including leucopenia and has twice the likelihood of being rejected [59] [60].

3.4. Epstein Barr Virus

Epstein Barr Virus (EBV) is a herpes virus and therefore has characteristics that include double stranded linear DNA [61]. The capsid of EBV is an icosadeltahdron consisting of 162 capsomers surrounded by an envelope [61]. The receptor CD21 is primarily responsible for infection of B cells, causing continuous cell proliferation. This continuous cell proliferation can cause immortalization of B cells. During this process, there are several

EBV related proteins that can be found within infected B cells. In the nucleus of infected B cells, initiating events which lead to proliferation associated with cellular DNA synthesis occurs in addition to the formation of EBV-determined nuclear antigens (EBNAs). Although the function of EBNAs remains primarily unknown, there are six different proteins that comprise the EBNA which include EBNA-1, EBNA-2, EBNA-3A, EBNA-3B, EBNA-3C, and leader protein [61].

The clinical manifestation of an acute EBV infection (mononucleosis) includes fever, fatigue, cervical lymph node enlargement, and pharyngitis. Two clinical presentations that prevail in EBV infections include a sore throat and the development of malaise, myalgia, and fatigue. Adolescent and young adults in developed countries are more likely to contract mononucleosis but the reasoning behind this is not entirely understood.

Diagnosing mononucleosis cannot rely on symptoms alone. Heterophile antibody test is the practical way of diagnosing an EBV infection. Mammalian erythrocyte from various species are used in the heterophile tests in order to detect IgM class antibodies. This method of detecting EBV has its drawbacks since it is not likely to find EBV in patients 4 years or younger since they have not developed heterophile antibodies. Heterophile antibodies are also not very specific and can lead to false positives since other infections, malignancies, and autoimmune disease can lead to similar results as an EBV infection. VCA IgM, VCA IgG and EBNA-1 IgG specific antibody tests measured primarily from enzyme immunoassay platform are more specific than the heterophile antibody test. Reports of false positives have occurred using this assay [62]. It is important to note that EBNA-1 antibodies are not produced on the onset of the EBV infection and usually occur at 90 days or longer.

Although there is no definitive treatment for an EBV infection, there is some literature suggesting an off label use of acyclovir. The course of treatment is unknown and to our knowledge there are no drugs currently in the pipeline to treat EBV infections.

3.5. Human Herpes Virus 6

Human herpes virus 6 (HHV-6) is a member of the *β*-herpesvirus subfamily within the *Roseolovirus* genus and are divided into either HHV-6A or HHV-6B variants. The morphological features are similar to other herpes virion particles with a size ranging from 160 nm to 200 nm. The genome of HHV-6A can range from 159 kbp to 170 kbp in length while the genome for HHV-6B is about 162 kbp in length. The homology of HHV-7 is similar to that of HHV-6 with the exception of three genes which are specific to HHV-6; U22, U83, and U94. Differences between HHV-6A and HHV-6B include restriction endonuclease cleavage sites, properties associated with variation in tropism *in vitro*, and specificity of monoclonal antibodies given the difference in epitopes [63]-[65].

Most patients contract HHV-6 at an early age and primary infections in adulthood are rare. Roseola infantum is characterized by a maculopapular rash on the infant's trunk and neck with fever that last for approximately 3 - 5 days with temperatures often reaching 102˚F - 104˚F. In adults with primary infections a patient can experience mononucleosis-like fatigue in addition to elevated liver enzymes (1 - 3 weeks), sore throat, and cervical lymphadenopathy [66] [67]. Other serious illnesses in adults can include fulminant hepatitis and meningoencephalitis [68]. HHV-6 can become reactivated in the immunocompromised. This usually causes patients to have increased antibody titers and a higher level of DNA retrieved via PCR but tend to be asymptomatic. Other patients are likely to experience mild illness with the presentation of a rash and a mild fever [69]-[71].

Methods for detecting the presence of HHV-6 including indirect serological approach or the direct approach have their advantages and disadvantages. Indirect serology involves IFA, ELISA, and avidity assays. An advantage to these methods includes the ease of use and the accessibility of these techniques. A disadvantage includes a cross-reactivity with other betaherpesviruses, the inability to distinguish between HHV-6A and HHV-6B, and delayed response in the immunocompromised. Direct methods include viral cell culture, antigen detection, and various PCR methods. Advantages for cell culture include direct evidence of infectious virus and the ability to engage in precise investigation of the strain of the virus. Disadvantages include limited sensitivity, high cost, and a more labor intensive method compared to all other direct and indirect methods. The advantages to antigen detection include being able to differentiate from HHV-6A and HHV-6B, provide evidence of the gene expression of the virus, and the equipment used is conventional. Limited sensitivity and ambiguity of current standards for the approach are some of the disadvantages of antigen detection. PCR methods for detecting and distinguishing HHV-6A and HHV-6B tend to be highly sensitive and specific. However, these methods can have limitations in distinguishing between active and latent since specific thresholds for active and latent infections are ambiguous.

Treatment for HHV-6 with acyclovir for immunocompetent patients is 400 mg orally every 8 hours for seven

to fourteen days. IV acyclovir involves a 5 mg/kg dose every eight hours for seven to fourteen days. For patients who experience episodic outbreaks, 200 mg of acyclovir every four hours is recommended for seven to fourteen business days. Phosphonoformic acid can be used off label and may involve a 60 mg/kg/dose at a constant rate for over at least one hour for every eight hours for two to three weeks. Cidofovir can also be used off label at 5 mg/kg IV infusion once a week for two consecutive weeks before a maintenance dose of 5 mg/kg IV infusion once every two weeks.

3.6. *Streptococcus pyogenes*

Streptococcus pyogenes is characterized as Gram-positive catalase-negative aerobic bacterium that is arranged in chains. The M protein on its outer layer reacts with various host proteins, inhibits the deposition of complements, has a pro-inflammatory response, and contributes to mucosal adhesion [72]. The genome of *Streptococcus pyogenes* is highly plastic. Intragenic and intergenic recombination associated with horizontal gene transfer has been observed and is of particular interest with regard to emm gene diversity [73].

It is important to differentiate symptoms of a *Streptococcus pyogenes* infection to that of a viral infection. Symptoms of Streptococcus pyrogene infections include fever, sore throat, tonsillitis, cervical lymphadenopathy, and tonsillar exudate. Other symptoms that can persist include headache, abdominal pain, nausea and vomiting, scarlet fever, loss of appetite, and general discomfort. Viral infections can have co-occurring symptoms including a runny nose, cough, hoarseness, eye redness, muscle aches, and diarrhea.

Laboratory tests should be the primary means of diagnosing a Streptococcus pyrogene infection since the clinical presentation is nonspecific. The two predominant methods of diagnosis involve either a throat culture or a rapid antigen-detection test from a specimen captured by a throat swab. The results of culturing *Steptococcus pyrogene* from a throat swab take approximately one to two days before a conclusive finding can be accepted respectively. Although rapid antigen-detection is significantly more expensive to run, the results of the test are significantly faster and can be obtained within minutes.

Treatment of Streptococcal pharyngitis often relies on the use of penicillin and its derivatives. 500 mg of Penicillin V two or three times a day for ten days or 50 mg/kg of Amoxicillin (with a maximum of 1 g) once a day for ten days are the predominate method of treating Streptococcal pharyngitis. Patients with allergies to penicillin and its derivatives should take either Cephalexin, Cefadroxil, Azithromycin, or Clindamycin. 20 mg/kg/dose of Cephalexin taken orally twice daily for 10 days, 30 mg/kg of Cefadroxil once a day for 10 days, 12 mg/kg of Azithromycin once a day for 5 days, or 7 mg/kg/dose of Clindamycin three times a day for 10 days are the recommended dosages for treating Streptococcal pharyngitis. Maximum tolerated dosages do apply to each of these medications and therefore careful consideration should be taken for individuals with higher weights.

4. Mycotoxin

Although exposure to mycotoxins is rare in patients with chronic Lyme disease complex, there have been several instances where patients being treated for Lyme disease have also been exposed to mycotoxins. As the name suggest, mycotoxins are toxic secondary metabolites produced by a few fungal species that are known to colonize crops. The amount of species of fungi that produce mycotoxins is vast and therefore not listed independently. Instead, various mycotoxins are listed with their effect on the mammalian system as well as the methods for detecting the mycotoxins in various matrices of contaminated food. The word mycotoxin stems from the Greek word “myke” which means fungus and the Latin word “toxicum” which means poison. Secondary metabolites of fungus are not always harmful. Significant advances in the treatment of bacterial infections stemmed from secondary metabolites of fungal species. However, there are several mycotoxins that have a major negative effect on humans.

Mycotoxins are characterized by their small molecular weight ranging around a MW of 700. The structural and chemical diversity of mycotoxins are vast. The majority of mycotoxins are a result of chemical reactions associated with metabolites including acetates and pyruvates in particular. Such diversity also leads to varying levels of toxic effects that can be either acute or chronic. Contamination of mycotoxins can occur before harvest or after harvest. This is particularly true for plants that have been stored for more than a few days. Commonly contaminated food includes dried fruit, coffee, spices, cocoa, oil seeds, beans, dried peas, cereal, nuts, and apples in particular. More information regarding the methods of detecting mycotoxins in various food sources can be seen in **Table 1**.

Table 1. The table below is a list of common mycotoxins, their effect on the mammalian system, where the mycotoxins can be found, and the protocol for a method of detecting the mycotoxins within a matrix.

Toxin	Major effects on mammalian systems	Protocol	Matrix	Reference
Aflatoxins	Acute hepatitis, impaired immune system, carcinogenic	UV-HPLC	Brazilian peanut kernels	[74]-[78]
Citrinin	Nephrotoxic	Time resolved luminescence (TRL)	Soft cheese	[79] [80]
Moniliformin	Weight loss, intestinal hemorrhage, Keshan disease	Normal-HPCL	Cereals	[80]-[84]
Ochratoxin A	Carcinogenic, hepatotoxic, teratogenic, nephrotoxic	Membrane based flow through enzyme immunoassay	Cereals	[74] [85]
Patulin	Lung and brain haemorrhaging	Micoremulsionelectrokinetic chromatography (MEECK)	Commercial apple juice	[86] [87]
Trichothecene	Gasroinestinalhaemorrhaging, immuno-depressant	HPLC analysis after supercritical fluid extraction (SFE)	Wheat	[88]-[91]
Zeralenone	Estrogenic Activity	Normal-HPCL	Cereals	[92]

5. Discussion

It is critical to treat Lyme disease at its early stages since *Borrelia burgdorferi* has the potential to protect itself from antibiotics and the immune system through various mechanisms if given ample time to spread throughout the body. Many patients do not recall getting bit by a tick and many patients do not receive the characteristic bull's eye skin formation. The diagnostic criteria for detecting Borrelia can also be problematic. This leads to patients obtaining chronic Lyme disease that is not easily treated by antibiotics alone. To make things worse, many patients experience symptoms associated with co-infections and secondary co-infections.

Awareness of doctors to quickly recognize the symptoms of Lyme disease as well as the awareness to differentiate the symptoms associated with co-infections is critical. Improper diagnosis or even partial diagnosis of Lyme disease and their associated co-infections can lead to serious complications that can lead to hospitalization and even death. Powassan virus in particular is of concern since there is no readily available method to diagnose or treat the disease. More research is absolutely needed for the Powassan virus since even the most fundamental aspects of the Powassan virus remain a mystery.

The most common co-infections, including anaplasmosis, babesiosis, bartonellosis, and ehrlichiosis, are all treatable with antibiotics. However, although treatment is necessary and can be safely administered, the additional antibiotics to treat these co-infections of Lyme disease is an additional burden on the body. These co-infections are significantly easier to treat than chronic Lyme disease but it is important to note that the health of the patient is significantly worse than those with only Lyme disease. It is important to not only recognize and diagnose the co-infections but to also treat the root of their disease rather than treating the symptoms.

6. Conclusion

The list of secondary co-infections is not by any means exhaustive. Opportunistic infections can occur with or without additional co-infections to patients with chronic Lyme disease, further complicating treatment. It is important to monitor patients with Lyme disease in order to reduce the likelihood of contracting an opportunistic infection including diagnosing and treating previously asymptomatic diseases if and when they occur. Complications such as exposure to mycotoxins highlight the significance of being aware of various factors that can impact a patient's health that is not usually associated with Lyme disease. Chronic Lyme disease patients also need immune system monitoring to help maintain long term immune surveillance and to decrease the re-occurrence of these infections.

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