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RESEARCH ARTICLE

LYME BORRELIOSIS: A REVIEW

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ABSTRACT

Lyme Borreliosis is a complex disease which varies in its clinical presentation, thus can be difficult to diagnose. The classic clinical diagnosis of Lyme disease is erythema migrans rash, however, literature has shown not all patients who develop Lyme disease develop this characteristic. The life cycle, pathogenicity and ecological interactions that have an impact on the risk of transmission are multifaceted and require further research. Infection prevention and control of Lyme disease hinge on physician and public education regarding personal protection measures, symptoms and signs of the disease as well as appropriate antibiotic treatment. Early and consistent approaches to diagnosis appear essential to infection prevention and control within primary care. Increasing public awareness and concerns about Lyme disease and its potential consequences for an individual is required. Evidence also necessitates the requirement for more intensive screening within blood and blood component part transfusion. However, there is an overall lack of research within this area as highlighted by referring to seminal research studies within the text. On evaluation, if the figures for Lyme disease continue to rise, further vaccines may be required to control the outbreaks of a potentially harmful disease.

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INTRODUCTION

Lyme Borreliosis or Lyme disease is a zootonic infection caused by the bacteria Borrelia burgdorferi which is transmitted to humans by the bite of an infected tick in the UK. Lyme Borreliosis is the most common tick-borne infectious disease in Europe (Rauer *et al*., 2020). Other bacterium'sassociated with Lyme Borreliosis include Borrelia afzelii and Borrelia garinii (Kullberg *et al*., 2020; Stanex *et al*., 2012). At least 85,000 people in Europe and 300,000 people in the United States are infected with Lyme Borreliosis each year (Schotthoefer and Frost, 2015).Public Health England (2018) reports there are approximately 1,000 serology confirmed cases in England and Wales. The prevalence of the Lyme Borreliosis is increasing worldwide (Streere *et al*., 2004), and an increasing number of reported cases are on the rise in Scotland and the rest of the UK. However, many cases of Borrelia burgdorferi go unreported as the clinical manifestations are so diverse (Kullberg *et al*., 2020; Schotthoefer and Frost, 2015). Scotland like many other countries around the world are increasing surveillance as a matter of public health. Lyme Borreliosis or Lyme disease is a notifiable condition under Public Health (Scotland) Act (2008). At present, there is no known cure for Lyme Disease (Fletcher, 2019).

However, vaccines have been used in the past but subsequently withdrawn in 2002 due to constraints in public spending (Streere and Glickstein, 2004; Girschick *et al*., 1996). Modes of transmission for Lyme disease spirochete are under speculation, and therefore pose an additional threat to infection and prevention control in a global context. Infection, prevention and control (IPC) methods are currently being revised globally due to a substantiated increase in confirmed cases.

Lyme Borreliosis: Lyme Borreliosis is a tick-borne bacterial infection which can be transmitted to humans through sustaining a bite from an infectious lxodes Ricinus tick. Ticks share a similar visual appearance to small spiders and can be found commonly in undergrowth and on bushes in gardens, parks and the countryside. Ticks sustain off the blood of rodents, birds and deer which are the common reservoir for Borrelia burgdorferi, however, they are also known to bite humans. Ticks can also contract Borrelia burgdorferi from contaminated animals (Fletcher, 2019). Once infected they can transmit Borrelia burgdorferi to a human by biting them (Biesiada *et al*., 2012). Ticks are most commonly found in hard-to-reach areas such as the scalp, axilla and groin but have been known to attach to any part of the human body. There is some debate within research as to how long the infected tick

needs to be attached to a human before infection occurs, ranging between 2 –72 hours (Streere *et al*., 2004; Brown *et al*., 2003; Hefty *et al*., 2002). The Centre for Disease Control (CDC) (2021) suggest the probability of infection increases with the length of time of human exposure to the tick, which approaches 100% on the third day.

Microbiology of Borrelia burgdorferi: As previously discussed, the scientific name for Lyme Disease is Borrelia burgdorferi. As a spirochaetal form of bacteria maintained through nature; it is a slow growing gram-positive bacterium (Motaleb *et al*., 2015). The borrelial genome is unique in structure, organization, and copy number (Rosa, 1997).

Symptoms and Differential Diagnosis: Lyme disease according to Berglund *et al*., (1995) most often presents with the development of "a distinctive circular rash, known as erythema migrans, at the site of the tick bite". Research has shown that the incubation period is between 3 to 32 days (Biesiada *et al*., 2012; Streere *et al*., 2004). On physical appearance, the rash is commonly visually compared to looking like a bull's eye on a dart board. The physical manifestations are pictured in Appendix 1. Erythema migrans usually becomes visible within 4-6 weeks although evidence has shown it may appear anywhere from 3 days to 3 months after being bitten, lasting for many weeks (NICE, 2020).

Literature reports as many as a third of all cases fail to notice a rash but might present with other manifestations including flu-like symptoms, fatigue, muscular aches and pains, joint pain, neck stiffness, headaches, fever and chills (Kullberg *et al*., 2020; Stanek *et al*., 2011). Tertiary levels of the clinical manifestations can be localised, disseminated or chronic as shown within Appendix 2. Research has indicated, late-stage disease can develop months, if not years later, if Borrelia burgdorferi is left untreated or if treatment is delayed (Ronsefield *et al*., 2005). Presentations include inflammatory arthritis, nerve problems, cardiac problems, meningitis and encephalitis (Kullberg *et al*., 2020; Ogrinc *et al*., 2016; Hansen *et al*; 1992). Long-term health problems may also occur presenting similarly to fibromyalgia and chronic fatigue syndrome (Kullberg *et al*., 2020). Co-infections from other micro-organisms have also been detected in lxodes ticks (Wagemakers *et al*., 2015; Vannier *et al*., 2012) however,co-infections are deemed as relatively rare (Strle *et al*., 2014; Steere *et al*., 2003). Co-infections if present, are noted to change the path of acute Lyme Borreliosis increasing the duration and the gravity of the symptoms (Thomar *et al*., 2001; Krause *et al*., 1996). Predominant researchers emphasise it is important to note some symptoms of Lime Disease are non-specific, thus clinicians should consider a variety of different diagnoses. Methods to determine diagnosis include serology, synovial fluid aspirations or biopsy, lumbar puncture for cerebrospinal fluid analysis, Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) Scan (NICE, 2020; Fletcher, 2019; Biesiada *et al*., 2010).

Laboratory Diagnosis: The National Institute for Clinical Excellence (NICE) offers guidance, and clinical advice on Lyme Disease, outlining the steps for diagnosis. Antibiotic treatment is the core method of managing Lyme disease. However, several studies highlight antibiotic therapy to have different efficacy outcomes, all of which are poorly defined within studies (NICE, 2018). The development of a 'core outcome set'is currently stressed as high priority to enable comparisons across trials in order to strengthen results through meta-analysis. NICE (2018) recognise methods should be patient centred and include patient involvement on the measurement of priority outcomes. At present, there is insufficient evidence on the efficacy of treatment regimens and the cost effectiveness of treatments. NICE (2020) advocate using clinical trials for dosages and strengths when studying the efficacy between oral and intravenous treatments. Serological antibody tests and biomarkers are the dominant laboratory tests for Lyme Disease. A 2-tiered testing system is currently practiced within the UK. An initial positive result on an enzyme-linked immunosorbent assay (ELISA) leads to a confirmation immunoblot test. Supporting evidence suggests combined 1g/G1gM ELISA based on the IR6 peptide and immunoblotcan be effective, however, this researchhas not been completed within the UK and is deemed as low-quality in accordance with the hierarchy of evidence (Streere *et al*., 2004).

There is arguably substantial evidence to say laboratory testing is not always necessary for those with erythema migrans due to the specific rash pattern, and as treatment is known to prevent further symptoms developing (Streere, 2001). However, testing is beneficial for patients presenting with other symptoms to ensure accurate diagnosis and appropriate treatment is obtained. Prompt treatment is important with Lyme Borreliosis to prevent the progression of the infection. NICE (2018) advocate repeating serology testing to ensure an immune response has been given enough time to develop. Children's immune response may not be as rapid as an adult but at present no substantiated evidence highlights that Bb differentiates between children and adults. Referral to an appropriate specialist may be necessary if symptoms persist. NICE (2020) advocates the need for further research to study the serology and non-serology over the natural course of the disease. NICE (2020) state this "may assist the interpretation of patients who remain symptomatic and those who are at high risk of reinfections through occupational exposure".

Recommendations for IPC Management

Recommendations for the management of Lyme disease currently aim to standardise antibiotic treatment and provide a consistent framework for good practise (NICE, 2018). However, prescribing practises and guidelines are subject to change which may be subsequently altered according to new evidence. At present, the treatment for Bb is one course of antibiotics (NICE, 2020). Treatments for ongoing symptoms are vague and practice differs across the globe. Peer reviewed research indicates that further antibiotic treatment is a justifiable recommendation if there is a possibility of a continuing infection, despite receiving previous treatment (NICE, 2020). Nevertheless, in recent research conducted by Sharma *et al*., (2015) Bb was established as persistent demonstrating the ability to evade antibiotics.

Public Health: The sprirochetal agent of Lyme disease according to Stricker, Lautin and Burrascano (2006) is "one of the most complex bacteria known to man", thus representing a growing public health threat. As a modern public health strategy, Holland (2015) recognises the vital importance of disease prevention in promoting good health, reducing harm through education, using treatment as a preventive measure, and adequately identifying infected individuals. Similarly, NICE(2018) recommend 'improving the awareness of Lyme

disease to promote early investigation and treatment in order to optimise health outcomes'. This may be achieved by raising clinician awareness about the possibility of Lyme disease spirochete. As a public health strategy to raise awareness, frontline staff such as nurses, GP's, and those involved with primary care play a key role in the early diagnosis and management, therefore require access to educational resources to keep informed on the identification and emerging management of Lyme disease. This knowledge is key in reducing the bacterium and controlling the infection for the patient. Incremental costs from testing and treatment for this according to NICE (2018) can be balanced by the advantages of enhanced recognition and early treatment in controlling the disease. Promoting awareness of tick and tick-borne infections amongst patients is a crucial step within IPC and public health (Public Health England, 2012). Public health campaigns such as how to safely remove an attached tick are essential in lowering the risk of developing Lyme disease through the presence of Bb. Personal protection methods such as protective clothing, repellents or acaricides, regular tick checks and landscape modifications are advocated methods of infection prevention and control which can help break the chain of infection (Hayes *et al*., 2005).

Vaccination: A previous vaccine was developed in the 1990's (Recombinant OspA Vaccine) which was proven to be effective for the prevention of Lyme disease in the United States (Streere at al, 1998). However, acceptance by physicians and the public was limited. This, added to the high cost of the preventative approach in comparison to the cost of antibiotic treatment early in the infection, led to it being withdrawn by the manufacturer in 2002(Streere and Glickstein, 2004; Girschick *et al*., 1996).

Transmission Mechanisms: The transference of Lyme disease is associated through tick bites however, other modes of transmission have been controversially questioned. Various studies show that transmission can take place through other modes than ticks. The presence of Bb has been found in mosquitos, fleas and mites and other blood sucking insects (Herzer *et al*., 1986; Doby *et al*., 1985).Transplacental transmission has been raised in numerous studies, identifying that mother to child in utero transmission has taken place (Gardner, 2001). A further mode of transmission is through contact with infected urine and other bodily fluids from infected animals (Shaw *et al*., 2005). Transference of Bb spirochetes through sexual transmission has also been found in vaginal and semen secretions; emphasising that borrelia in store semen is able to survive crypto preservation (Middlevein *et al*., 2015; Bach 2001; Diaka and Harris, 1995). Transmission via blood, tissue and organ donation is also noted to be possible (Herwaldt *et al*., 2011) and will be discussed more in-depth within the next section.

Borrelia spirochetes detection in blood transfusion: At present no incidence of Lyme disease has been associated with blood transfusion, however, scientists have discovered that Lyme disease bacteria are able to live in blood from a person with an active infection which is stored for donation (CDC, 2021; Pavia and Plummer 2018; Johnson *et al*., 1990). It is recommended that individuals who are receiving treatment for Lyme disease with antibiotics should not donate blood (CDC, 2021). However present guidelines as stipulated by the CDC (2021) recommend patients who have completed antibiotic treatment for Lyme disease can still be deemed to be potential blood donors. It is noted that the risk of acquiring a transfusion-transmitted infection within the UK has significantly reduced over the last few decades (NHS Blood and Transplant/Public Health Epidemiology Unit, 2014). However, the possibility that the transfer of Lyme disease spirochete through blood transfusion has arguably been debated within clinical research. Seminal studies completed by Wormser *et al*., (2005;2001) and Pavia and Plummer (2018; 2013) detected the presence of live blood borne Borrelia in the peripheral vascular system in adults with an erythema migrans rash who were yet to receive antibiotic therapy. Research has distinguished that the spread of spirochete occurs early in the illness particularly in symptomatic patients, however, many individuals who are infected can remain asymptomatic, posing a theoretical risk (Cameron, 2021). Seminal work completed by Wormser *et al* (2001) detected the presence of Borrelia with in the vascular system from 2 to 5 weeks and beyond. This raises the concern that a blood transfusion from a spirochetemic donor may unknowingly transmit Lyme disease through a blood or component parts transfusion (Ginzberg *et al*., 2013). Further fundamental seminal research conducted by Johnson *et al*., (1990) into the survival of experimentally infected human blood with Bb processed for transfusion, identified that Lyme spirochetes could survive the normal blood bank storage procedures. Furthermore, in a recent study conducted by Munro *et al*., (2015) into the seroprevalence of Lyme Borreliosis in Scottish blood donors, concluded that out of 1440 serum samples, 4.2% of blood donors exhibited positive Borrelia serology thus highlighting the need for more in-depth screening.

Due to the ethical implications, transferring potentially infectious blood to healthy human volunteers within an experimental study is not viable. However, experimental studies in rodents have shown Bb can be transferred from spirochetemic donor mice to healthy mice suggesting transmission of the pathogen is possible (Cameron, 2021; Thorp *et al*., 2016; Gabitzsch *et al*., 2006). This experiment closely mirrored human blood transfusion procedures and highlights the need for approved diagnostic methods for monitoring blood products for possible contamination of Lyme disease spirochete, especially in geographical areas where Bb infections and other tick-related diseases are evident (Pavia and Plummer, 2018).

Conclusion

Lyme Borreliosis is a complex disease which varies in its clinical presentation, thus can be difficult to diagnose. The classic clinical diagnosis of Lyme disease is erythema migrans rash, however, literature has shown not all patients who develop Lyme disease develop this characteristic. The life cycle, pathogenicity and ecological interactions that have an impact on the risk of transmission are multifaceted and require further research. Infection prevention and control of Lyme disease hinge on physician and public education regarding personal protection measures, symptoms and signs of the disease as well as appropriate antibiotic treatment. Early and consistent approaches to diagnosis appear essential to infection prevention and control within primary care. Increasing public awareness and concerns about Lyme disease and its potential consequences for an individual is required. Evidence also necessitates the requirement for more intensive screening within blood and blood component part transfusion. However, there is an overall lack of research within this area as

highlighted by referring to seminal research studies within the text. On evaluation, if the figures for Lyme disease continue to rise, further vaccines may be required to control the outbreaks of a potentially harmful disease.

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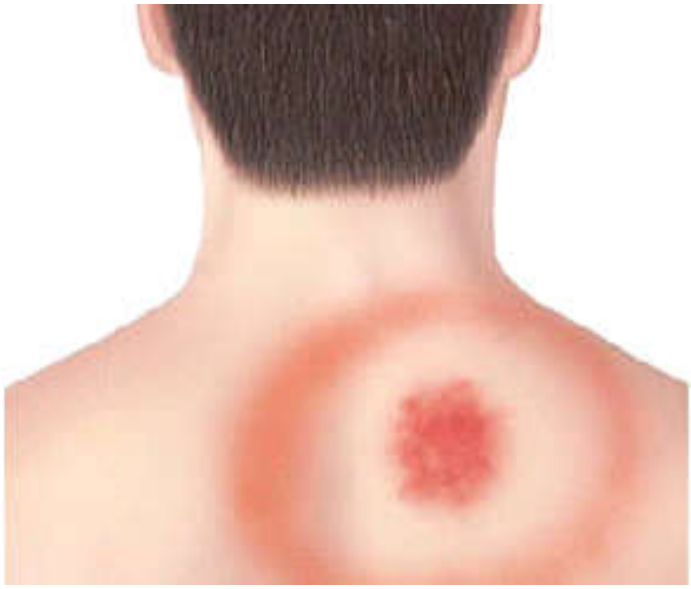
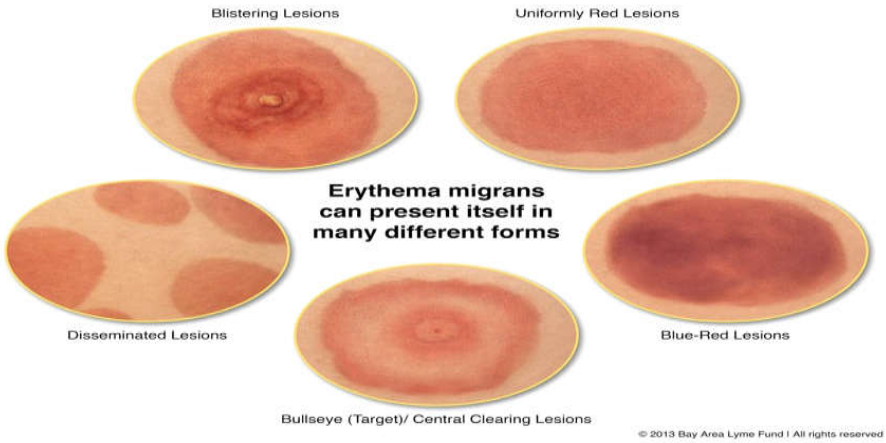
Appendix 1

Pictures below illustrate Erythema migrans





Appendix 2

Clinical Features of Lyme Borreliosis

SYSTEM	STAGE 1 (Early) Localised	STAGE 2 (Early) Disseminated	STAGE 3 (Late) Chronic
Skin	Erythema migrans	Secondary annular lesions	
Musculoskeletal	Myalgia, arthralgia	Migratory pain in joints, brief arthritis attacks	Prolonged arthritis attacks, chronic arthritis
Neurological	Headache	Meningitis, Bell Palsy, cranial neuritis, radiculoneuritis	Encephalopathy, polyneuropathy, leukoencephalitis
Cardiac		Atrioventricular lock, myopericarditis, pan carditis	
Constitutional	Flu like symptoms	Malaise, fatigue	Fatigue
Lymphatic	Regional lymphadenopathy	Regional or generalised lymphadenopathy	

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