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6

### Arthropod-borne arthritides



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Infections with several types of viral and bacterial pathogens are able to cause arthritic disease. Arthropod vectors such as ticks and mosquitoes transmit a number of these arthritis-causing pathogens, and as these vectors increase their global distribution, so too do the diseases they spread. The typical clinical manifestations of infectious arthritis are often similar in presentation to rheumatoid arthritis. Hence, care needs to be taken in the diagnoses and management of these conditions. Additionally, clinical reports suggest that prolonged arthropathies may result from infection, highlighting the need for careful clinical management and further research into underlying disease mechanisms.

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#### Introduction

Considerable evidence indicates that pathogens are a significant trigger of rheumatic disease. Infection with viral pathogens such as human immunodeficiency virus, coxsackievirus B, cytomegalovirus, rubella virus, adenovirus, Epstein–Barr virus, parvovirus B19, alphaviruses and dengue virus, and bacterial pathogens such as *Borrelia*, *Rickettsia* and *Pasteurella* can all lead to rheumatic manifestations. The most common causes of infectious arthritis worldwide are arthropod-borne, being transmitted through the bite of an infected mosquito or tick. Alphaviruses, which include chikungunya

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virus (CHIKV), Sindbis virus (SINV) and Ross River virus (RRV), are transmitted by mosquitoes, and they cause arthritis, arthralgia and myositis often persisting for weeks or months with symptoms being severe at onset and often self-limiting. Lyme disease is a rheumatic illness resulting from an infection with a bacterial spirochete of the *Borrelia* species, and it is transmitted by certain ixodid ticks.

The mosquito-borne alphaviruses, from the *Togaviridae* family, are positive sense, single-stranded ribonucleic acid (RNA) viruses that consist of a genome encoding four non-structural and five structural proteins, packaged into a nucleocapsid and surrounded by a lipid bilayer containing the glycosylated envelope proteins. Alphaviruses are distributed throughout the world, and they are generally classified as arthritogenic or encephalitic viruses. The arthritogenic alphaviruses include RRV, CHIKV, SINV, o'nyong nyong (ONNV), Semliki Forest virus (SFV), SINV, mayaro virus (MAYV) and Barmah Forest virus (BFV).

The *Borrelia* genus of bacteria includes 36 spirochete species, 12 of which are known to cause Lyme disease. The three main causative agents are *Borrelia burgdorferi*, *Borrelia afzelii* and *Borrelia garinii* with the main tick vectors being the blacklegged tick or deer tick (*Ixodes scapularis*), and the western-blacklegged tick (*Ixodes pacificus*). Traditional symptoms of Lyme disease include fever, headache, fatigue and a characteristic skin rash called erythema migrans, and, if left untreated, the infection can spread to the joints causing severe arthritic disease.

The increasing incidence and severity of infectious forms of arthritic disease highlights the urgent need for the development of cost-effective and efficacious treatments and control measures. Combining clinical data with ongoing scientific research has proved invaluable in improving our current understanding of the mechanisms of disease pathogenesis; however, there are still considerable gaps in current knowledge. This review discusses the current understanding of infectious arthritides, particularly in the areas of clinical disease and pathogenesis, highlighting areas of future focus.

## Tick-borne arthritis

### Lyme disease

#### Background

Lyme disease is a zoonotic, tick-borne illness transmitted by specific ixodid ticks to humans. With approximately 300,000 cases per annum, Lyme disease is the most common reportable vector-borne disease in the United States [1]. The most common presenting clinical feature is a skin lesion called erythema migrans [2]. In the United States, Lyme disease is caused only by the spirochete *B. burgdorferi*, whereas in Europe and Asia, *B. afzelii* and *B. garinii* are also clinically important [3]. In the United States, it is transmitted by *I. scapularis* ticks, often referred to as deer ticks, in the northern and Midwestern states and by *I. pacificus* ticks in the western states. In Europe and Asia, the main vectors are *Ixodes ricinus* and *Ixodes persulcatus*, respectively. This is in accordance with the incidence rate of erythema migrans, which peaks during the spring and summer months [1]. Risk factors for Lyme disease include occupational and recreational exposure to fields and woods in endemic areas, as well as outdoor activities such as gardening on residential properties near woodlands [4]. Ixodid ticks are also known to be vectors for other diseases that may produce co-infection with *B. burgdorferi*, which can show clinical manifestations from asymptomatic to severe and life threatening [5].

Although more cases are diagnosed during the summer months, infections can occur throughout the year. Individuals of all ages are susceptible to Lyme disease; however, the disease has a bimodal distribution: it is most common amongst children between the ages of 5 and 9, and adults between the ages of 55 and 59. More than half of the cases occur in men (53.1%) [6]. Only 30,000 cases are reported to the Centers for Disease Control (CDC) each year; however, according to the CDC, cases are under-reported with approximately 300,000 individuals infected in the United States each year [1]. The incidence rate continues to increase, may be due to better surveillance and increased awareness or to a higher infection rate from more frequent travel to endemic areas.

#### Clinical disease presentation

There are three distinct infection phases of Lyme disease: early localised, early disseminated and late disseminated. All phases have overlapping features [7]. The early localised phase begins with an

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