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# Viral arthritis

## Background

Arthralgia is a common presentation to general practice, and many cases will not require any specific treatment. It is important to differentiate viral arthritis from other causes as early intervention in inflammatory arthritis has been shown to improve long-term outcome.

## Objective

This article provides a review of the different causes of viral arthritis, with an emphasis on recognising the clues to a viral cause, and summarises appropriate investigations and management.

## Discussion

Viral arthritis is typically self-limiting and requires no specific intervention, although in rare cases symptoms can be prolonged. Some viruses have a predilection for the joints, and arthritis is one of the common presenting signs of infection. It may also be a manifestation of important treatable viral infections such as hepatitis and human immunodeficiency virus (HIV). Early systemic inflammatory arthritis can be difficult to differentiate from viral arthritis and should be actively considered in all patients. Comprehensive testing for viral aetiologies is of limited utility.

## Keywords

arthritis/rheumatic diseases; viruses; Ross River virus; diagnosis, differential



Arthritis or arthralgias are common presentations to general practice. Many cases are self-limiting and are presumed to be due to viral infections. However, rheumatoid arthritis (RA) and other types of systemic inflammatory arthritis may be difficult to differentiate from viral arthritis, yet require early intervention to improve long-term outcomes. Some serious but treatable viral infections, such as hepatitis and HIV, may present with joint symptoms, and it is axiomatic that these conditions should be identified and managed appropriately. Some viral infections may cause more prolonged symptoms and their recognition, and particularly differentiation from early inflammatory arthritis, is important in determining prognosis. This article focuses on the clinical features and recognition of different types of viral arthritis, and provides guidance on investigations, referral and treatment.

## Clinical presentations and course

### Epstein-Barr virus (EBV)

EBV infections are typically asymptomatic, reflected in the high rates (80%) of people with IgG antibodies directed at EBV.<sup>1</sup> However, when acute infections do occur, all will have memorable pharyngitis and 95% will have cervical adenopathy. Arthritis is relatively rare and does not occur in isolation, although widespread myalgias are common. Other herpes viruses, such as cytomegalovirus (CMV), herpes simplex virus (HSV) and varicella zoster virus (VZV) are unusual causes of arthritis.<sup>2</sup>

### Adenovirus and enterovirus

Adenovirus rarely causes arthritis and is usually acquired asymptotically or manifests as respiratory tract or gastrointestinal infection.<sup>2</sup> Similarly, enteroviruses (Coxsackie virus and echoviruses) may have protean manifestations, most typically non-specific febrile illness, aseptic meningitis, pleurodynia or exanthems. They are most unlikely to present with isolated joint manifestations.

### Parvovirus B19

Parvovirus B19 infections in children present as a viral exanthema, and in adults as a cause of arthralgia and arthritis. The incubation period is 7–10 days with non-specific flu-like symptoms in the first



week followed by arthralgias or arthritis in up to 60% of patients in the second week. Up to 75% of adults will have a rash, although only 20% will have the typical 'slapped cheek' appearance.<sup>3</sup> The hands, feet and knees are commonly affected, usually symmetrically. Pain, rather than swelling, is the dominant feature. A dramatic decrease or absence of reticulocytes is a hallmark laboratory finding. Rarely, joint symptoms persist for months or years, but the arthritis is non-destructive.

## Hepatitis A

In its prodromal phase, hepatitis A infection in adults usually presents with flu-like symptoms. The infection then progresses to the icteric phase, which may include jaundice, bilirubinuria, pruritus and abdominal pain. Arthralgias and rash occur in 10–14% of patients, but arthritis is extremely rare.<sup>4</sup>

## Hepatitis B (HBV)

HBV infection may be asymptomatic, but symptomatic patients will develop constitutional symptoms in the prodromal period. During this period, HBV-infected hosts can develop a sudden-onset, transient polyarthritis (involving the wrists, knees, ankles and small joints of the hands) that may mimic the onset of RA, although typically accompanied by a rash. The arthritis usually subsides at the onset of jaundice.<sup>5</sup>

## Hepatitis C (HCV)

HCV infection is usually asymptomatic but can present with acute hepatitis, nausea and abdominal pain. HCV infection becomes chronic in about 80% of patients and is usually asymptomatic or manifests with mild, non-specific symptoms.<sup>6</sup> Polyarthralgias occur in approximately 20% of patients with chronic HCV and an inflammatory oligoarthritis or polyarthritis (mimicking RA but not destructive) occurs in 2–5% of patients. Chronic HCV infection is associated with abnormal immune function, including cryoglobulinemia and positive rheumatoid factor, leading to potential diagnostic confusion. It is important to exclude HCV in RA patients as HCV infection can be exacerbated by immunosuppressive therapy.

## Human immunodeficiency virus (HIV)

Early HIV infection may be asymptomatic or present with a variety of non-specific symptoms and signs, including constitutional symptoms, adenopathy, pharyngitis and frequently a rash. Arthralgias and arthritis are present in 5.5% of people with HIV.<sup>7</sup> Acute HIV-associated arthritis tends to be self-limiting, lasting less than 6 weeks. It will usually present as oligoarticular or polyarticular, with negative tests for antinuclear antibodies and rheumatoid factor. Established HIV infection is associated with a number of rheumatic syndromes that fall outside the scope of this review.

## Ross River virus (RRV) and Barmah Forest virus (BFV)

RRV and BFV are arthritogenic alphaviruses and are transmitted by mosquito vectors with intermediate hosts.<sup>8</sup> They are responsible for

5000–8000 Australian cases of polyarthritis annually, with decreasing prevalence from north to south, although changing land practices and climate change are likely to influence this distribution. RRV is most common among adults aged 25–44 years and there is equal sex distribution.<sup>9</sup> The incubation period is 2–10 days with a characteristic sudden onset of illness.<sup>8</sup> The symptoms are typically non-specific and include polyarthralgia (85–98% of patients), myalgia (60%), rash (50%, typically maculopapular and more common and florid in BFV) and fever (35–50%); half to two-thirds of patients are asymptomatic. Joint symptoms and signs are usually symmetrical and acute in onset, and ankles, fingers, wrists and knees are most commonly affected. Effusions are often present and the distribution can be similar to that seen in polyarticular RA.<sup>9</sup> The erythrocyte sedimentation rate (ESR) can be transiently elevated but C-reactive protein is rarely increased. The arthropathy typically resolves within a few weeks to a few months. Almost all patients with symptoms beyond 6 months have other conditions, such as osteoarthritis, autoimmune arthritides and depression, that account for their disease.<sup>10</sup>

## Measles, mumps and rubella

Rubella classically presents with a maculopapular rash on the face that spreads to involve the trunk, hands and feet, sparing the palms and soles, accompanied by significant head and neck lymphadenopathy. Rubella and rubella vaccine are associated with arthritis, which occurs in 30–50% of females and 6% of males.<sup>11</sup> The arthritis is similar to that in rheumatic fever and the small joints of the hands, wrists and the knees are most commonly involved. Arthralgia is much more common than frank arthritis, and peri-articular involvement is frequently seen. The arthritis typically starts in the week before and after the onset of rash and usually resolves within 2 weeks. Arthritis with mumps is extremely rare, with small or large joint synovitis within 4 weeks of parotitis. Symptoms can persist for up to several weeks.<sup>12</sup> Arthritic presentations of measles virus have not been described.<sup>13</sup>

A summary of the clinical presentations of viral arthritis is given in *Table 1*.

## Early inflammatory arthritis

Patients presenting with early inflammatory arthritis, particularly those with RA, have long-term benefits from the early institution of disease-modifying therapy. The suspicion of RA is raised by several clinical features (*Table 2*). These patients benefit from early specialist referral. The utility of investigating patients with early, undifferentiated arthritis for viral causes has been assessed in a large, early arthritis cohort.<sup>14</sup> Where arthritis had persisted for more than 6 weeks, the prevalence of previously unknown arthritogenic viral infection was 0.25% for parvovirus, 0% for HBV and HIV, and 0.37% for HCV. Routine screening was therefore not recommended. In Australia, RRV may also be associated with a more persistent arthritis, but the utility of screening similar patients is unknown. Although suspected of contributing to the triggering of rheumatic disease, there is no evidence that viruses cause autoimmune disease or destructive arthritis.



**Table 1. Clinical presentations of viral arthritis**

Virus	Frequency of arthritis	Typical presenting features	Likelihood of presenting with arthritis	Duration of arthritis	Comments
EBV	Very low	<ul style="list-style-type: none"> <li>• Pharyngitis, cervical lymphadenopathy</li> <li>• Fevers</li> </ul>	Very low	Days	Often have myalgias with acute infection
Herpes viruses	Very low	<ul style="list-style-type: none"> <li>• CMV – infectious mononucleosis</li> <li>• VZV – chicken pox/shingles</li> <li>• HSV mucosal infections</li> </ul>	Very low	N/A	Rarely associated with arthritis. Specific treatments indicated for some non-articular manifestations
Adenovirus and enterovirus	Very low	<ul style="list-style-type: none"> <li>• Upper respiratory tract infections, gastrointestinal symptoms, conjunctivitis</li> </ul>	Very low	N/A	
Parvovirus B19	High	<ul style="list-style-type: none"> <li>• Viral exanthem in children</li> <li>• Arthritis/arthralgia in adults with preceding febrile illness</li> </ul>	High	Days but may be prolonged for months	Diagnosis assisted by concurrent demonstration of IgM and IgG antibodies
Hepatitis A	Low	<ul style="list-style-type: none"> <li>• Flu-like illness followed by jaundice</li> </ul>	Low	Days	Arthralgia more common than frank arthritis
Hepatitis B	Moderate	<ul style="list-style-type: none"> <li>• Malaise, rash, jaundice</li> </ul>	Moderate	Days/weeks	Arthritis is abrupt in onset, in RA distribution preceding icteric phase
Hepatitis C	Moderate	<ul style="list-style-type: none"> <li>• Malaise, jaundice</li> </ul>	Moderate	Weeks, months in chronically infected patients	Chronic arthralgia (20%); true arthritis (2–5%)
HIV	Low	<ul style="list-style-type: none"> <li>• Acute infectious mononucleosis-like illness at seroconversion in some patients.</li> </ul>	Low		Arthritis, arthralgia with acute infection. Increased incidence of several rheumatic diseases in chronic infection
RRV	Very high	<ul style="list-style-type: none"> <li>• Arthralgia, myalgia, rash, fever</li> </ul>	Very high	Weeks to months	Diagnosed by demonstration of seroconversion. Can rarely be associated with prolonged arthritis
Mumps	Very low	<ul style="list-style-type: none"> <li>• Parotitis and lymphadenopathy</li> </ul>	Very low	Weeks	
Rubella	High	<ul style="list-style-type: none"> <li>• Acute maculopapular rash, sparing the palms and soles</li> </ul>	High	Weeks	Can occur with rubella vaccine

## Establishing the diagnosis

Viral arthritis is typically associated with symptoms of a flu-like illness and systemic signs such as a viral exanthem, fever and lymphadenopathy, and these features should be sought on history and examination. Most presentations are with a polyarthritis; a monoarthritis should prompt investigation for other aetiologies. The presence or absence of extra-articular features of an autoimmune disease should also be elicited. Confirmation of a recent viral infection requires an appropriate change in paired serology (Table 3)<sup>15</sup>. Given the high rate of infections in the general population (as with EBV), positive IgG antibodies alone are non-diagnostic. Similarly, IgM antibodies do not always represent recent infection as they can persist for up to 2 years.<sup>16</sup> Testing for antinuclear antibodies,

rheumatoid factor and anti-citrullinated protein antibodies (ACPA) is useful in evaluating people with typical or persistent presentations of inflammatory arthritis, but are neither sufficiently sensitive nor specific to make diagnoses alone. Viral arthritis can be associated with rheumatoid factor, although this is usually at low titre and transient. There are a number of differentials for a polyarthritis; however a full discussion of these is beyond the scope of this review.

Specific testing for viral arthritis is indicated if treatable diseases are suspected on the basis of the clinical picture (such as HCV or HIV), or when reassurance is important. As both RRV and BFV are notifiable diseases in Australia, a serological diagnosis should be made if the clinical suspicion is high. Routine screening for all potential arthritogenic viruses is not advised.



**Table 2. Features suggesting rheumatoid arthritis**

- Symptom duration of longer than 6 weeks
- Early morning stiffness for longer than one hour
- Arthritis in three or more regions
- Bilateral compression tenderness of the metatarsophalangeal joints
- Symmetry of areas affected
- Rheumatoid factor positive
- Anti-cyclic citrullinated peptide (anti-CCP) antibody positive
- Bony erosions evident on X-rays of the hands or feet (uncommon in early disease)
- Family history of inflammatory arthritis

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**Table 3. Criteria for serological diagnosis of an acute viral infection (requires a change between acute and convalescent serology)<sup>15</sup>**

Acute serology	Convalescent serology
IgM+ and IgG–	IgM+ and IgG+
IgM– and IgG–	IgM+ and IgG+
IgM+ and IgG–	IgM– and IgG+
Or a 4-fold increase in paired serology tests	

## General treatment

Viral arthritis that has been evident for less than 6 weeks is treated symptomatically. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the mainstay of treatment. The potential benefits of NSAIDs should be weighed up against their potential risks. It is essential to provide reassurance to the patient that the symptoms are self-limiting and unlikely to develop into a serious condition, such as RA, or cause joint destruction or disability. The use of corticosteroids is to be discouraged unless there are troublesome symptoms and contraindications to NSAIDs, or where a brief course of low dose (<10 mg of prednisone daily) may be reasonable.

## When to refer

Specialist referral for acute viral arthritis is rarely needed. It should be considered when arthritis persists beyond 6 weeks, where an early inflammatory arthritis such as RA is suspected or where investigation results are ambiguous or inconsistent with the clinical findings. Patients with suspected HIV, HBV or HCV may also benefit from specialist referral.

## Key points

- Viral arthritis is typically self-limiting and requires no specific intervention.

- Arthritis may be a manifestation of an important treatable viral infection, such as hepatitis or HIV.
- Some viruses have a predilection for the joints and result in prolonged symptoms.
- Early systemic inflammatory arthritis can be difficult to differentiate from viral arthritis and should be actively considered in all patients.

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