# Parvovirus Infection in Children with Reactive Arthritis

**Thesis**
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# Table of abbreviations

| Abbreviation | Word |
|---|---|
| AIDS | Acquired immunodeficiency syndrome |
| ASOT | Anti-streptolysin O titre |
| B١٩ | Parvovirus B١٩ |
| CBC | Complete blood count |
| CRP | C reactive protein |
| DNA | Deoxyribonucleic acid |
| EBV | Epstein-Barr virus |
| ELISA | Enzyme-linked immunosorbent assay |
| ESR | Erythrocyte sedimentation rate |
| Hb | Hemoglobin |
| HIV | Human immunodeficiency virus |
| IFN | Interferon |
| Ig | Immunoglobulin |
| IL | Interleukin |
| NSAIDs | Non-steroidal anti-inflammatory drugs |
| NS١ | Nonstructural protein |
| PCR | Polymerase chain reaction |
| RBCs | Red blood corpuscles |
| ReA | Reactive arthritis |
| RNA | Ribonucleic acid |
| VP | Viral protein |
| WBCs | White blood cells |

# INTRODUCTION

Infections have been associated with arthritis during their course and as a post-infectious reaction observed several weeks or months afterwards. Although certain infectious organisms have been suspected but not proved to trigger juvenile rheumatoid arthritis, other agents are often associated with a transient arthritis that does not satisfy the classification criteria for juvenile rheumatoid arthritis ***(Miller and Cassidy, ٢٠٠٣b).***

Reactive arthritis follows an infection outside the joint, particularly the gastrointestinal or genitourinary tract. The course of reactive arthritis is variable and may progress to chronic spondyloarthropathy. Post-infectious arthritis implies arthritis that follows infections that are usually viral in origin, with shorter duration than reactive arthritis ***(Miller and Cassidy, ٢٠٠٣b).***

Reactive arthritis can be secondary to direct invasion of the joint space or to immune mechanisms (subsequent to or concomitant to an infection). Among viral infections including parvovirus B١٩ and others (e.g. Epstein-Barr virus) have been reported so, in patients with acute arthritis, the presence of preceding infections should always be investigated ***(Cimaz et al., ٢٠٠٥).***

# AIM OF WORK

To study the role of parvovirus infection in the pathogenesis of reactive (post-infectious) arthritis in children and its effect on the clinical manifestations and the acute phase reactants. And to investigate the role of Epstein-Barr virus in children with reactive arthritis.

# Reactive Arthritis

Reactive arthritis is an aseptic arthritis that is triggered by an infectious agent located outside the joint ***( Amor, ١٩٩٨ ).*** It is an acute spondyloarthropathy that usually follows a uro-genital or enteric infection, often in patients positive for the HLA-B٢٧ antigen ***( Kiratiseavee and Brent, ٢٠٠٤).***

Reactive arthritis falls under the rheumatic disease category of seronegative spondyloarthropathies, which includes ankylosing spondylitis, psoriatic arthritis, the arthropathy of associated inflammatory bowel disease, juvenile onset ankylosing spondylitis, and juvenile chronic arthritis ***(Kohnke, ٢٠٠٤).***

Reiter syndrome -arthritis, urethritis/cervicitis, and conjunctivitis-is now considered a subset of reactive arthritis. In ١٩١٦, Hans Reiter described the classic triad of arthritis, non-gonococcal urethritis, and conjunctivitis (Reiter syndrome). More recently, Reiter syndrome also has been defined as a peripheral arthritis lasting longer than ١ month, associated with urethritis, cervicitis, or diarrhea ***( Fan and Yu, ٢٠٠١).***

The term reactive arthritis was first introduced to describe the association between Yersinia enterocolitica infection and arthritis, and it was intended to differentiate this form of acute, non-suppurative arthritis, which is characterized by negative joint culture, from infectious, purulent arthritis; the differentiation was meant to suggest an underlying sterile immune mediated pathomechanism ***(Ahvonen et al., ١٩٦٩).***

A few years later, the term reactive arthritis was related to HLA B٢٧; at this time the term was more strictly applied to the HLA-B٢٧ associated reactive arthritides, following infections with enterobacteria and Chlamydia ***( Aho et al., ١٩٧٣).***

This concept has been widely recognized and accepted. However, non-HLA-B٢٧ associated arthritides, such as Lyme disease induced by Borrelia burgdorferi, Neisseria gonorrhoeae induced reactive arthritis and post-streptococcal reactive arthritis are viewed presently as reactive arthritides. This inclusion is based on the observation that these arthritides also develop after a primary extra-articular infection, and that despite negative culture results, the organisms can be detected in the joint ***(Liebling et al., ١٩٩٤ and Jaulhac et al., ١٩٩٦).***

This brief historical outline demonstrates not only the changing definition of "reactive arthritis" over time, but also illuminates the lack of general consensus concerning the precise clinical and scientific conditions to which this term should be applied, and the lack of consensus as to how to differentiate reactive from infectious arthritis ***(Kuipers et al., ١٩٩٩).***

## Epidemiology:

In the US overall (in adults and children) frequency is estimated as ٣,٥-٥ cases per ١٠٠،٠٠٠ males with higher frequency following nonspecific urethritis. Prevalence of inapparent Chlamydia infections may make incidence even higher ***(Cush and Lipsky, ٢٠٠١).*** In the United Kingdom, the incidence of reactive arthritis after urethritis is about ٠,٨٪. The incidence of HLA-B٢٧ is higher among the Finnish population, so, occurrence appears to be related to the prevalence of HLA-B٢٧ in a population and the rate of urethritis/cervicitis and infectious diarrhea ***(Cush and Lipsky, ٢٠٠١).***

Reactive arthritis and symptoms of Reiter syndrome were reported After outbreaks of Salmonella enteritidis ***(Dworkin et al., ٢٠٠١).*** Reactive arthritis incidence is high among patients with AIDS ***(Lin , ١٩٨٨).***

While ***Thatayatikom and Kurahara (٢٠٠٢)*** reported that patients with reactive arthritis have been described in all racial groups; no racial predisposition is known, ***Scoggins and Boyarsky (٢٠٠٤)*** said that it is reported most frequently in whites.

Reactive arthritis is most prevalent in boys, with male-to-female ratio is ٤:١ ***( Thatayatikom and Kurahara, ٢٠٠٢).***

Reactive arthritis has been reported in patients of all ages, some as young as ٢ years, although most pediatric patients present with symptoms after age ٩ years. The Peak onset is in persons aged ١٥-٣٥ years. Its true frequency in childhood is difficult to determine and it is almost entirely postenteric ***(Cuttica et al., ١٩٩٢ and Ansell, ١٩٩٤).***

## Etiology :

A healthy but genetically predisposed individual develops reactive arthritis (ReA) after a suitable triggering infection. Most commonly the initial infection has affected the digestive or the urogenital tract and the terms enteroarthritis or uroarthritis are used, respectively ***(Toivanen and Toivanen, ١٩٩٥).***

Multiple organisms can trigger ReA mostly following a genitourinary infection or infectious enteritis. The clinical picture following any of these conditions is virtually identical. Chlamydia trachomatis infection is the most common antecedent of reactive arthritis. Bacteria triggering reactive arthritis and the resulting manifestations at the entry site are shown in **Table ١** ***(Arnold and McKenna, ١٩٩٤), (Toivanen and Toivanen, ١٩٩٥), (Braun et al., ١٩٩٧), (Hudson et al., ١٩٩٨) and (Toivanen, ١٩٩٨).***

Several viruses can cause ReA, they are listed in **Table ٢** ***(Miller and Cassidy, ٢٠٠٣b).***

Chronic reactive arthritis may follow enteric infection with non-typhoidal Salmonella, Shigella, Yersinia enterocolitica, Campylobacter jejuni, Cryptosporidium parvum, or Giardia intestinalis, or genitourinary tract infection with Chlamydia trachomatis ***(Miller and Petty, ٢٠٠٣).***

## Pathogenesis:

Reactive arthritis usually develops ٢-٤ weeks after a genitourinary or gastrointestinal infection. Recent evidence indicates that a preceding respiratory infection with Chlamydia may also trigger the disease. About ١٠٪ of patients do not have a preceding symptomatic infection ***( Braun et al., ١٩٩٤).***

After detection of antigens from various bacterial species known to trigger reactive arthritis (for example, Chlamydia trachomatis, Salmonella enteritidis, Yersinia enterocolitica) in synovial fluid and tissue, the hypothetical process of pathogenesis was viewed primarily as a sterile immune mediated synovitis with dead bacteria, or non-proliferating antigens, present in the joint tissue ***(Bas et al., ١٩٩٥).***

**Table ١:** Bacteria triggering reactive arthritis-manifestations at the entry site

| Site of entry | Clinical manifestations | Bacteria |
|---|---|---|
| gastrointestinal tract | diarrhea | *Yersinia enterocolitica |
| | gastroenteritis | *Salmonella typhimurium |
| | enterocolitis | *Shigella flexneri |
| | oligo- and asymptomatic infection | *Campylobacter jejuni/fetus |
| | | *Clostridium difficile |
| | | (via changes of intestinal flora) |
| | | Brucella abortus/mellitensis |
| urogenital tract | urethritis, cystitis | *Chlamydia trachomatis |
| | cervicitis | Ureaplasma urealyticum |
| | prostatitis, epididymitis | Mycoplasma hominis |
| | salpingitis, endometritis | Neisseria gonorrheae |
| | often asymptomatic infection | Bacille Calmette-Guerin |
| | | Gardnerella vaginalis |
| Broncho-pulmonary tract | bronchitis, pneumonia, sinusitis | Chlamydia pneumoniae |
| | angina tonsillaris | β-hemolytic streptococci |
| | tuberculosis | Mycobacterium tuberculosis |
| skin/mucosa | erythema chronicum migrans | Borrelia burgdorferi |
| | acrodermatitis chronica atrophicans | |
| | skin infections, joint infections | Staphylococcus aureus |
| | cat-scratch disease | Bartonella |
| | brucellosis | Brucella abortus/mellitensis |
| | leptospirosis | Leptospira |

* Reactive arthritis triggering bacteria associated with HLA-B٢٧.

***(Arnold and McKenna, ١٩٩٤), (Toivanen and Toivanen, ١٩٩٥), (Braun et al., ١٩٩٧), (Hudson et al., ١٩٩٨) and (Toivanen, ١٩٩٨)***