**Post-Infectious Reactive Arthritis: A Systematic Review of the Literature on Reiter's Syndrome**

**ABSTRACT**

**Aims:** This study aims to systematically review the clinical manifestations, diagnostic approaches, and therapeutic strategies associated with post-infectious reactive arthritis, also known as Reiter’s Syndrome. It explores the role of infectious agents and genetic susceptibility (HLA-B27), as well as the implications of multidisciplinary management in improving outcomes.

**Study Design:** Systematic literature review.

**Place and Duration of Study:** Databases searched (PubMed, SciELO, LILACS, BVS, MEDLINE) between April and May 2025.

**Methodology:** The review followed PRISMA guidelines. Descriptors used included “Reactive Arthritis,” “Reiter Syndrome,” “Diagnosis,” “Treatment,” and names of associated pathogens. Inclusion criteria were studies published between 2015 and 2024, including observational studies, reviews, and case reports focusing on clinical, diagnostic, or therapeutic aspects of the disease.

**Results:** Reactive arthritis is most often triggered by *Chlamydia trachomatis*, *Salmonella*, *Shigella*, *Yersinia*, or *Campylobacter*. Common symptoms included asymmetric oligoarthritis, enthesitis, urethritis, conjunctivitis, and skin lesions like circinate balanitis. Diagnosis remains clinical, aided by HLA-B27 testing and pathogen identification. NSAIDs were the first-line treatment, while DMARDs were used for chronic or severe cases. Antibiotic use was controversial, especially in the absence of active infection. A multidisciplinary approach proved essential for managing systemic and extra-articular symptoms.

**Conclusion:** Post-infectious reactive arthritis presents consistent clinical patterns and requires early clinical suspicion, particularly in young adults with a recent infection. NSAIDs and DMARDs form the therapeutic backbone, but further research—particularly randomized trials—is needed to refine diagnostic and treatment protocols.

1. **INTRODUCTION**

Reiter's Syndrome, currently recognized as post-infectious reactive arthritis, is a form of inflammatory spondyloarthritis that occurs following genitourinary or gastrointestinal infections, and is classically characterized by the triad of arthritis, urethritis, and conjunctivitis. Not all patients present with the complete triad. It is an immune-mediated condition, strongly associated with the HLA-B27 antigen, and most commonly affects young adult males. Symptoms typically begin weeks after the initial infectious episode and may progress to persistent joint involvement, in addition to variable mucocutaneous and ocular manifestations (1).

In clinical practice, reactive arthritis represents a relevant differential diagnosis for acute inflammatory arthritis in young adults. Early identification can be challenging due to the lack of a specific diagnostic test and variability in clinical presentation, particularly in women, who tend to exhibit milder or oligosymptomatic forms. Epidemiologically, its incidence is directly linked to the prevalence of triggering infections such as Chlamydia trachomatis, Shigella, Salmonella, Yersinia, and Campylobacter. The presence of HLA-B27 is not only associated with increased severity but may also influence chronic disease progression in certain populations (1).

Although it is a relatively well-known condition, there is a lack of systematic reviews consolidating recent knowledge on its clinical manifestations, diagnostic strategies, and therapeutic approaches [13-15]. Reactive arthritis spans multiple medical specialties — including rheumatology, urology, ophthalmology, and infectious diseases — which often leads to a fragmented approach in clinical practice. Furthermore, inconsistencies in terminology, such as the continued use of the term "Reiter's Syndrome," can hinder literature searches and interpretation of findings. In the context of rising antimicrobial resistance and emerging atypical infectious agents, there is an urgent need to reassess the available evidence to guide more effective disease management (2,16,17).

Thus, the aim of this systematic review is to address this gap by providing a critical analysis of recent literature on the condition. The central research question is: “What are the clinical manifestations, diagnostic approaches, and therapeutic strategies described in scientific literature over the past 10 years regarding Reiter’s Syndrome (post-infectious reactive arthritis)?” The answer to this question is intended to offer updated and clinically relevant insights to improve the multidisciplinary management of the disease and help standardize care in a condition that is often underrecognized.

1. **MATERIAL AND METHODS**

**Research Question**

This systematic review was guided by the following research question, structured according to the PICO model:

* P (Population): Individuals diagnosed with reactive arthritis (Reiter’s syndrome);
* I (Intervention): Available diagnostic and therapeutic strategies;
* C (Comparison): Not applicable;
* O (Outcomes): Clinical characterization, diagnostic methods used, and reported therapeutic approaches.

**Guiding question:**
*What are the clinical manifestations, diagnostic approaches, and therapeutic strategies described in scientific literature over the past 10 years regarding Reiter’s Syndrome (post-infectious reactive arthritis)?*

**Data Sources and Search Strategy**

The search was conducted between April and May 2025 in the following scientific databases: PubMed, SciELO, LILACS, BVS, and MEDLINE. There were no geographic or language restrictions, but only articles published between 2015 and 2024 were considered.

The following descriptors and MeSH terms were used in combinations adapted to each database's syntax:

* “Reactive Arthritis”;
* “Reiter Syndrome”;
* “Artrite Reativa”;
* “Síndrome de Reiter”;
* “Diagnosis”;
* “Treatment”;
* “Clinical Manifestations”;
* “Etiology”;
* “Chlamydia”;
* “Salmonella”;
* “Yersinia”;
* “Campylobacter”;
* “Urethritis”;
* “Conjunctivitis”.

The search strategy applied Boolean operators AND and OR, as exemplified below:
("Reactive Arthritis" OR "Reiter Syndrome") AND ("Diagnosis" OR "Treatment") AND ("Clinical Manifestations")

**Inclusion and Exclusion Criteria**

**Inclusion criteria:**

* Articles published between January 2015 and April 2025;
* Original studies, systematic reviews, narrative reviews, case reports, or case series focusing on reactive arthritis or Reiter’s syndrome;
* Studies addressing clinical manifestations, diagnosis, or treatment of the condition;
* Full-text articles available.

**Exclusion criteria:**

* Studies that did not mention reactive arthritis as a primary focus;
* Articles focused exclusively on post-viral arthritis (e.g., SARS-CoV-2, HIV, arboviruses) without association with classical reactive arthritis criteria;
* Duplicate records across databases;
* Editorials, letters to the editor, or opinion articles without clinical data.

**Time Frame Considered**

Only articles published between **January 2015 and April 2025** were included, aiming to gather recent and relevant evidence reflecting the latest advances in diagnosis and treatment of reactive arthritis.

**Article Screening Process**

The study selection followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A total of 250 records were initially identified through electronic database searches. After removing duplicates (n = 46), 204 records were screened based on titles and abstracts. Of these, 170 were excluded for not meeting the inclusion criteria. The remaining 34 articles were assessed in full, resulting in the exclusion of 22 studies for not directly addressing reactive arthritis or lacking relevant clinical data. In the end, 12 studies were included in the qualitative synthesis. The complete screening and selection process is illustrated in the PRISMA flowchart.

FIG 1. Flow chart showing study protocol

Studies included in quantitative synthesis (meta-analysis)
(n = 12)

Studies included in qualitative synthesis
(n = 12)

Full-text articles excluded, with reasons
(n = 22)

Full-text articles assessed for eligibility
(n = 34)

Records excluded
(n = 170)

Records screened
(n = 204)

Records after duplicates removed
(n = 204)

Additional records identified through other sources
(n = 0)

## Identification

## Eligibility

## Included

## Screening

Records identified through database searching
(n = 250)

**Methodological Quality Assessment**

The methodological quality of included studies was assessed based on their respective study designs. For case reports and case series, a checklist adapted from the Joanna Briggs Institute (JBI) was used. For systematic reviews, the AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews) instrument was applied.

As most included studies were observational or descriptive in nature, criteria were applied with a focus on clarity of objectives, methodological transparency, case descriptions, and consistency between findings and conclusions. Studies deemed of low quality or lacking sufficient information were excluded.

1. **RESULTS**

**TABLE 1. Main characteristics of the studies included in the systematic review**

| **Author (Year)** | **Study Type** | **Country** | **Main Infectious Agent** | **HLA-B27** | **Clinical Manifestations** | **Therapeutic Strategies** |
| --- | --- | --- | --- | --- | --- | --- |
| Dey et al. (2021) [1] | Case report | India | *Leptospira interrogans* | Positive | Arthritis, uveitis | NSAIDs, corticosteroids |
| Taylor-Robinson & Jensen (2020) [2] | Systematic review | UK | Non-gonococcal urethritis | — | Urethritis, balanitis, arthritis | Clinical follow-up |
| Singh et al. (2017) [3] | Observational study | India | *Chlamydia*, *Salmonella* | Variable | Oligoarthritis, enthesitis | NSAIDs, DMARDs |
| Kiliç et al. (2018) [4] | Case report | Turkey | *Chlamydia trachomatis* | Positive | Uveitis, arthritis | Corticosteroids, DMARDs |
| Ferreira et al. (2015) [5] | Book chapter | International | Various | — | Classical triad | Multidisciplinary approach |
| Ivashkivskyi et al. (2021) [6] | Case series | Eastern Europe | *Yersinia enterocolitica* | — | Arthritis, enteritis | NSAIDs, diagnostic support |
| Nidavani et al. (2015) [7] | Narrative review | India | *Chlamydia*, enteric pathogens | — | Peripheral arthritis | NSAIDs, DMARDs |
| Papaliodis (2017) [8] | Book chapter | USA | — | — | Uveitis, arthritis | Immunosuppressants |
| García-Gil et al. (2020) [9] | Case report | Spain | — | — | Circinate balanitis | Symptomatic treatment |
| Schmitt (2017) [10] | Literature review | USA | *Chlamydia trachomatis*, others | Variable | Arthritis, urethritis | NSAIDs, antibiotics (if active infection) |
| Carney et al. (2015) [11] | Case report | UK | *Chlamydia trachomatis* | — | Circinate balanitis | Antibiotics, NSAIDs |
| Krajewska-Włodarczyk et al. (2015) [12] | Case report | Poland | *Salmonella* | — | Skin lesions | Multidisciplinary approach |

The studies included in this systematic review were published over the last decade, between 2015 and 2024, reflecting the current state of scientific literature on post-infectious reactive arthritis, traditionally known as Reiter's Syndrome. A wide geographical distribution was observed, with publications from different regions of the world, including countries such as the United States, the United Kingdom, India, Turkey, and Brazil. This diversity highlights the global interest in the condition, although there is a higher concentration of studies in countries with greater clinical research infrastructure.

Regarding study type, case reports and case series predominated, especially due to the rarity of the classic form of the condition and the often episodic nature of reactive arthritis. However, some observational studies and narrative reviews were also identified, addressing epidemiological, clinical, and therapeutic aspects of the disease in specific populations. No randomized clinical trials on the condition were found during this period, revealing a significant gap in the literature regarding evidence-based therapeutic management.

The populations studied were mostly composed of young adults, predominantly male, with a recent history of genitourinary or enteric infections. Some studies described clinical manifestations in HLA-B27 positive patients, reinforcing the role of this genetic marker in susceptibility to the condition. The heterogeneity of clinical manifestations among the studies also underscores the need for a multidisciplinary approach to the diagnosis and proper management of reactive arthritis.

**Etiology and Associated Infectious Agents**

Reactive arthritis is classically triggered by a previous infection in an extra-articular site, usually in the genitourinary or gastrointestinal tracts. The most frequently implicated infectious agents include Chlamydia trachomatis, in the context of urethritis, and enteric bacteria such as Salmonella, Shigella, Yersinia enterocolitica, and Campylobacter, all associated with episodes of infectious diarrhea or acute enterocolitis (3,4).

Atypical cases have also been reported in recent literature, such as infections by Leptospira interrogans and, more recently, post-COVID-19 articular manifestations, although these do not fit the classical criteria for reactive arthritis due to involving distinct pathogenic mechanisms (5,6). The HLA-B27 antigen is present in up to 80% of cases in some populations and is an important susceptibility marker, being associated with more severe, prolonged, or recurrent forms of the disease (7).

**Clinical Manifestations**

The clinical manifestations of reactive arthritis are broad and multisystemic. The articular pattern is predominant, usually presenting as an asymmetric oligoarthritis, mainly affecting the joints of the lower limbs—knees, ankles, and interphalangeal joints. Enthesitis, especially at the Achilles tendon, and dactylitis, characterized by diffuse finger swelling, are also common (7,3).

Extra-articular manifestations include urethritis, conjunctivitis, and, to a lesser extent, anterior uveitis. The latter can be severe and requires ophthalmologic follow-up, especially in HLA-B27 positive patients (8). In addition, cutaneous manifestations such as circinate balanitis and keratoderma blennorrhagicum, although rare, are highly specific and assist in clinical diagnosis (9). In chronic or recurrent cases, greater functional impairment is observed, mainly in the absence of early treatment (7).

**Diagnostic Methods Used**

The diagnosis of reactive arthritis is predominantly clinical, as there are no standardized and universally accepted laboratory criteria. A detailed clinical history, with emphasis on recent infection and typical joint symptoms, is essential. Pathogen identification by PCR or serology (mainly Chlamydia trachomatis or enteropathogens) is recommended, especially when there is consistent clinical suspicion (10,11).

Laboratory tests such as PCR, ESR, and complete blood count are useful for assessing systemic inflammation, although they are not specific. HLA-B27 typing, although not mandatory, can support the diagnosis, especially in cases with chronic progression or extra-articular manifestations (12). Regarding imaging, simple radiographs, joint ultrasound, and in some cases, magnetic resonance imaging are used to exclude other causes of arthritis or assess joint complications (6,12).

**Treatment Strategies**

The management of reactive arthritis involves multidisciplinary approaches focused both on reducing joint inflammation and controlling the underlying infection. Nonsteroidal anti-inflammatory drugs (NSAIDs) represent the first-line treatment, with good response in most cases, especially in acute and uncomplicated presentations (7,10).

In cases with persistent or moderate to severe symptoms, the use of corticosteroids, mainly intra-articular, is a common practice. For patients with polyarticular or significant extra-articular involvement, disease-modifying antirheumatic drugs (DMARDs) such as sulfasalazine and methotrexate are indicated (3,7). In refractory or chronic cases, biological agents such as TNF-alpha inhibitors have been successfully used, especially in HLA-B27 positive patients (8).

In the infectious context, antibiotic use is recommended when there is confirmation of active infection, especially by Chlamydia trachomatis. However, its benefit in late or already resolved cases is limited and controversial (10,18). There are also reports of complementary approaches, such as nutritional support, physiotherapy, and ophthalmologic follow-up in cases with uveitis (8,12).

**Outcomes and Prognosis**

In general, the prognosis of reactive arthritis is favorable, with symptom resolution within six months in most patients. However, about 20–30% may progress to chronic or recurrent forms, especially those who are HLA-B27 positive, have a history of recurrent infections, or exhibit severe extra-articular manifestations (3,7,8,19,20).

Factors associated with worse outcomes include the presence of uveitis, sacroiliitis, axial involvement, and lack of early treatment. In children and adolescents, there is a tendency toward spontaneous resolution, but clinical monitoring is necessary, as persistent forms may overlap with autoimmune juvenile arthritis (4,6). In adults, especially males with genitourinary infection by Chlamydia, the chance of recurrence or progression to axial spondyloarthritis is significantly higher (5,11).

Early diagnosis and an integrated multidisciplinary approach have been highlighted as essential to avoid structural complications and improve long-term patient quality of life (8,12).

1. **DISCUSSION**

The analysis of the studies included in this systematic review allowed the identification of recurring patterns in the clinical manifestations of reactive arthritis, as well as discussion of the degree of consensus regarding therapeutic strategies adopted across various clinical and population contexts.

**Observed Clinical Patterns**

The clinical manifestations of reactive arthritis were relatively consistent across studies, despite geographical and methodological differences. The most common presentation involved asymmetric oligoarthritis of the lower limbs, frequently accompanied by enthesitis (inflammation at tendon insertions, such as the Achilles tendon) and, in some cases, dactylitis (3,7). These manifestations are considered cardinal signs of the disease and were described both in adults and pediatric populations (4,12).

In addition to musculoskeletal involvement, a significant portion of patients presented extra-articular manifestations. Urethritis was predominant in cases associated with Chlamydia trachomatis, while conjunctivitis and anterior uveitis were more frequently reported in HLA-B27 positive patients (8,11). Another frequent finding was cutaneous involvement, especially circinate balanitis and keratoderma blennorrhagicum, which, although less prevalent, are highly specific for the condition (9).

An additional pattern observed was the association between HLA-B27 positivity and greater disease severity, including progression to chronic forms, presence of uveitis or sacroiliitis, and the need for more aggressive therapy (7,8). These findings reinforce the importance of considering HLA-B27 status as a prognostic rather than merely diagnostic marker.

**Consensus on Treatment Strategies**

Regarding treatment, the reviewed studies showed a high level of agreement on first-line approaches, particularly for managing articular symptoms. There is consensus that nonsteroidal anti-inflammatory drugs (NSAIDs) should be used initially, given their effectiveness in most acute and self-limited cases (3,7,10).

For persistent or severe cases, the use of corticosteroids, either orally or intra-articularly, was widely reported, although dosage and duration varied among studies. The introduction of disease-modifying antirheumatic drugs (DMARDs), such as sulfasalazine and methotrexate, was generally indicated for chronic or refractory cases, a point that also showed consensus among authors (7,8).

Conversely, there was divergence regarding the use of antibiotics. In cases with active Chlamydia trachomatis infection, antibiotics such as azithromycin or doxycycline were widely recommended. However, their use in patients without active infection remains controversial, being advised in some reports and discouraged in others, especially once arthritis is already established (10). Biological therapies such as anti-TNF agents were reported only in cases of therapeutic failure with conventional DMARDs and limited to case reports or small series, without robust long-term evidence of efficacy (8).

Another important point was the role of multidisciplinary management, particularly in cases with ophthalmologic or mucocutaneous manifestations. Studies emphasized the importance of shared evaluation with rheumatologists, infectious disease specialists, ophthalmologists, and, in some cases, dermatologists, as a strategy to avoid diagnostic delays and guide targeted therapies (8,12).

**Literature Gaps, Practical Implications, and Review Limitations**

One of the key findings of this review was the presence of significant gaps in the current literature on reactive arthritis, particularly in terms of methodological quality and study standardization. Most of the included works were case reports, case series, or narrative reviews, with a near-total absence of randomized controlled trials (3–12). This lack of high-level evidence hinders the development of stronger therapeutic recommendations and limits comparative assessment between management strategies.

Another major gap is the diversity of diagnostic protocols and inclusion criteria used across studies. Some authors consider only the classic triad (arthritis, urethritis, conjunctivitis), while others apply expanded definitions based on prior infection and joint symptoms. This lack of uniformity directly impacts the comparability of studies and the consistency of prevalence, severity, and treatment response estimates (3,7,10). Furthermore, few studies systematically assessed biomarkers or imaging tests, limiting the advancement of objective diagnostic criteria.

Despite these limitations, the findings presented have important practical implications for diagnosing and managing reactive arthritis. The identification of recurring clinical patterns—such as lower limb oligoarthritis, enthesitis, uveitis, and balanitis—can help non-specialist physicians recognize the condition in patients with recent genitourinary or enteric infections (3,4,7). Additionally, the consensus around the use of NSAIDs and, in more complex cases, DMARDs such as methotrexate or sulfasalazine, provides a therapeutic foundation that can be adapted to each clinical context (7,8,10).

This review also reinforces the importance of a multidisciplinary approach, especially in patients with systemic manifestations. Coordination among rheumatology, infectious diseases, ophthalmology, and dermatology can prevent diagnostic delays and allow for earlier, more targeted interventions, reducing the risk of chronicity and long-term sequelae (8,12).

Finally, this systematic review has its own limitations. First, there is a risk of publication bias, as studies with positive outcomes or unusual cases are more likely to be published. Second, although the search included international databases (PubMed, SciELO, LILACS, BVS, MEDLINE), most available studies were concentrated in specific regions, such as South America, Europe, and South Asia, which may limit the generalizability of the findings (3–12).

Additionally, the scarcity of standardized data hindered the execution of a quantitative meta-analysis, requiring instead a qualitative and descriptive synthesis. The absence of robust longitudinal data also restricts understanding of disease progression and long-term treatment effectiveness.

1. **CONCLUSION**

This systematic review demonstrated that reactive arthritis presents relatively consistent clinical patterns, with emphasis on lower limb oligoarthritis, enthesitis, and extra-articular manifestations such as conjunctivitis and urethritis. Diagnosis remains clinical and requires a high degree of suspicion, especially in patients with a recent infection.

In clinical practice, there is consensus on the use of NSAIDs as the initial treatment and DMARDs in persistent cases, although the role of antibiotics remains controversial. A multidisciplinary approach proved essential for appropriate management.

There is an urgent need for studies with greater methodological rigor, particularly randomized clinical trials and standardization of diagnostic criteria, in order to improve therapeutic strategies and follow-up for these patients.

**COMPETING INTERESTS DISCLAIMER:**

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

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