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***Urogenital Infection and Arthritis: Pathogenesis, Clinical Presentation, Diagnosis,
and Treatment – A Literature Review***

***Urogenitalinė infekcija ir artritas: patogenezė, klinikinis vaizdas, diagnozė ir
gydymas – literatūros apžvalga***

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1. Summary

Reactive arthritis is the most accepted form of arthritis in connection to urogenital infection and continues to be a clinically relevant but pathogenetically complex condition. Most commonly, it is associated with an infection of *Chlamydia trachomatis* and can lead to acute, recurrent or chronic inflammatory disease. Even with decades of research, there are still important challenges remaining, regarding the mechanisms of disease development, the differences in clinical manifestations, a lack of accepted diagnostic criteria that is universally accepted, as well as limited evidence that could guide advanced treatment strategies.

This thesis aims to synthesise and critically evaluate milestone studies and new evidence on arthritis and urogenital infection, with a special focus on reactive arthritis and its pathogenesis, clinical presentation, diagnosis and treatment. The main objectives were to summarise current evidence on pathogenesis, evaluate the clinical presentation, assess current diagnostic approaches, as well as their limitations and to review available therapeutic strategies and their effectiveness.

The design of this thesis was a narrative literature review with a structured literature search mainly in PubMed and Google Scholar, with an additional manual review of reference lists and specific author searches for publications by Prof. I. Butrimienė. “Reactive arthritis” was used as a mandatory keyword in the search process. Selection of publications was done according to the thematic relevance of pathogenesis, clinical presentation, diagnosis, treatment and a focus on literature from the last 10 years, also including older milestone studies if necessary.

The reviewed literature showed that reactive arthritis with urogenital infection is an inflammatory disease with multiple factors, in which persistent microbial components, dysregulated immune responses and host susceptibility interact closely. *Chlamydia trachomatis* is still the most strongly supported urogenital trigger. When looking at the clinical picture, the most typical findings is a patient with asymmetric oligoarthritis of the lower extremities, accompanied by symptoms such as enthesitis, dactylitis and extra-articular manifestations. Diagnosis is primarily clinical and can be supported by laboratory and microbiological findings as well as the exclusion of differential diagnoses. The treatment follows three steps and is individualised, with non-steroidal anti-inflammatory drugs forming the basis of the treatment, followed by glucocorticoids and conventional disease-modifying antirheumatic drugs and in selected refractory cases escalated to biological therapy. All in all, reactive arthritis is an infection-associated but immune-mediated disease with a high clinical variability and ongoing challenges regarding diagnostic, therapy and the pathogenesis of the disease. Further studies integrating microbiology, immunopathogenesis, clinical phenotype, treatment options and outcomes are needed.

Keywords: Reactive arthritis; urogenital infection; *Chlamydia trachomatis*; pathogenesis; diagnosis; treatment

2. Santrauka

Reaktyvusis artritas yra labiausiai pripažinta artrito forma, susijusi su urogenitaline infekcija, ir tebėra kliniškai reikšminga, bet patogenetiškai sudėtinga būklė. Dažniausiai jis susijęs su *Chlamydia trachomatis* infekcija ir gali sukelti ūminę, pasikartojančią ar lėtinę uždegiminę ligą. Net ir po dešimtmečius trukusių tyrimų vis dar išlieka svarbių iššūkių, susijusių su ligos vystymosi mechanizmais, klinikinių apraiškų skirtumais, visuotinai pripažintų diagnostinių kriterijų trūkumu, taip pat ribotais įrodymais, kurie galėtų padėti kurti pažangias gydymo strategijas.

Šios disertacijos tikslas – susintetinti ir kritiškai įvertinti svarbiausius tyrimus ir naujus įrodymus apie artritą ir urogenitalinę infekciją, ypatingą dėmesį skiriant reaktyviajam artritui ir jo patogenezei, klinikiniam vaizdui, diagnozei ir gydymui. Pagrindiniai tikslai buvo apibendrinti esamus patogenezės įrodymus, įvertinti klinikinį vaizdą, įvertinti dabartinius diagnostinius metodus, jų apribojimus ir apžvelgti galimas gydymo strategijas bei jų veiksmingumą.

Šio darbo dizainas buvo parengtas remiantis naratyvine literatūros apžvalga, atliekant struktūrizuotą literatūros paiešką daugiausia „PubMed“ ir „Google Scholar“ duomenų bazėse, o prof. I.

Butrimienė atliko papildomą rankinę literatūros sąrašų peržiūrą ir konkrečių autorių paiešką publikacijose. Paieškos procese kaip privalomas raktinis žodis buvo naudojamas „reaktyvusis artritas“. Publikacijos buvo atrenkamos pagal teminį patogenezės, klinikinio pateikimo, diagnozės, gydymo aktualumą ir daugiausia dėmesio skiriant pastarųjų 10 metų literatūrai, prireikus įtraukiant ir senesnius svarbius tyrimus.

Apžvelgta literatūra parodė, kad reaktyvusis artritas su urogenitaline infekcija yra uždegiminė liga, pasireiškianti daugeliu veiksnių, kurioje glaudžiai sąveikauja nuolatiniai mikrobiniai komponentai, sutrikęs imuninis atsakas ir šeimininko jautrumas. *Chlamydia trachomatis* vis dar yra labiausiai pagrįstas urogenitalinės infekcijos sukėlėjas. Vertinant klinikinį vaizdą, tipiškiausias požymis yra asimetrinis apatinių galūnių oligoartritas, lydimas tokių simptomų kaip entezitas, daktilitas ir ekstrasąnarinės apraiškos. Diagnozė pirmiausia yra klinikinė ir gali būti pagrįsta laboratoriniais ir mikrobiologiniais tyrimais, taip pat diferencinių diagnozių atmetimu. Gydymas susideda iš trijų etapų ir yra individualizuotas: gydymo pagrindas yra nesteroidiniai vaistai nuo uždegimo, po to gliukokortikoidai ir įprastiniai ligą modifikuojantys antireumatiniai vaistai, o kai kuriais atsparesniais gydymui atvejais pereinama prie biologinės terapijos. Apskritai reaktyvusis artritas yra su infekcija susijusi, bet imuninio atsako sukelta liga, pasižyminti dideliu klinikiniu kintamumu ir nuolatiniais iššūkiais, susijusiais su ligos diagnostika, gydymu ir patogeneze. Reikalingi tolesni tyrimai, apimantys mikrobiologiją, imunopatogenezę, klinikinį fenotipą, gydymo galimybes ir rezultatus.

3. Introduction

Urogenital infections are frequently encountered in clinical practice and can trigger not only local complications but also systemic inflammatory complications. One of the best recognised connections between these two is urogenital infection and arthritis, especially reactive arthritis, an inflammatory joint disease which develops after a preceding extra-articular mucosal infection, most commonly in the gastrointestinal or urogenital tract. Reactive arthritis currently is understood as a part of inflammatory spondyloarthropathies and has many of their clinical and pathogenetic features, such as asymmetric oligoarthritis, enthesitis, dactylitis, extra-articular manifestations and possible connections with HLA-B27 in common. Even though the strongest evidence is about bacterial triggers, especially gastrointestinal and urogenital pathogens, there have been discussions regarding a wider interpretation of reactive arthritis due to other infectious agents, including viral, and less commonly, other infection-related triggers. These above-mentioned connections regarding spondyloarthropathies and infectious agents have been known for decades, however, because of the heterogeneous presentation, its complex underlying mechanisms and the possibility of very variable disease courses it remains incompletely understood.(1,2)

A large proportion of publications have focused on urogenital infection-associated reactive arthritis in relation to *Chlamydia trachomatis*, which is seen as the most established urogenital trigger. In this context, *Chlamydia trachomatis* is not the only microorganism discussed. Other possible triggers of reactive arthritis can be other pathogens of the urogenital tract, such as *Ureaplasma urealyticum* and *Mycoplasma hominis*, as they have been detected in some reactive arthritis cohorts. However, their pathogenetic significance is less consistently established than *Chlamydia trachomatis*, as these organisms can also colonise the genitourinary tract without causing disease.(3–6)

Reactive arthritis is seen as an important clinical and scientific syndrome, as it links mucosal infection with immune dysregulation, genetic predisposition, as well as variable musculoskeletal and extra-articular manifestations in one clinical picture.(1)

Simultaneously, the disease remains challenging as it is heterogeneous regarding presentation and underlying mechanisms and consequently lacks a clear and universally accepted diagnostic criterion. The clinical relevance of this topic is clear, as it often affects young and middle-aged adults, has a risk for recurrent symptoms and chronicity, which can ultimately cause life-altering functional impairment in some patients. In addition to the initial urogenital manifestations, articular manifestations may highly disturb patients, as well as manifestations in eyes, skin as well as mucous membranes. This complicates the management and diagnosis and is a life limiting factor in affected adults, which needs a proper diagnosis and management that can be challenging due to the before mentioned factors.(1) Therefore, the importance of a structured and clinically oriented

review of the relationship between urogenital infection and arthritis is clear. Consequently, this thesis was done as a literature review of urogenital infection and arthritis, with a particular emphasis on reactive arthritis as the principal infection associated arthritic entity in this context. The aim of the review was to focus on the core aspects of pathogenesis, clinical presentation, diagnosis and treatment. Special attention was also given to publications by Prof. I. Butrimienė, as well as to literature focusing on broader infectious interpretations of reactive arthritis, additional urogenital pathogens and diagnostic approaches for the detection of *Chlamydia trachomatis* in women, as recommended by the supervisor. Furthermore, additional attention was given to literature which discuss pathogen detection in urogenital infection, which includes diagnostic approaches proposed for the identification of *Chlamydia trachomatis* in women. The aim of this thesis is to synthesise and critically evaluate the current evidence on the relationship between urogenital infection and arthritis, with distinct emphasis on reactive arthritis. The objectives of this study were to summarise the current evidence on the pathogenesis of reactive arthritis in the context of urogenital infection, to evaluate the clinical presentation of reactive arthritis associated with urogenital infection, to assess current diagnostic approaches as well as their limitations in reactive arthritis and to review available therapeutic strategies and their effectiveness in the management of reactive arthritis.

4. Methods

4.1. Study Design

The thesis was designed as a narrative literature review about the topic urogenital infection and arthritis, its relationship as well as its pathogenesis, clinical presentation, diagnosis and treatment with a focus on reactive arthritis. The aim was to synthesize and critically discuss current and longer known evidence on reactive arthritis, including important publications by Prof. I. Butrimienė. As the available literature on urogenital infection and arthritis or reactive arthritis is very heterogeneous, a narrative review design was chosen, and different types of publications were included, such as clinical studies, mechanistic investigations, observational studies and review articles. Because of the multiple factors that this topic includes, such as immunology, clinical observations, microbiology and therapeutic approaches, the narrative review design was best suited to use all evidence across these multiple dimensions of the topic. A systematic review could have also been used, but was disregarded as the purpose of this thesis was to develop a structured and clinically relevant overview of the topic rather than a quantitative summary of evidence. While searching for usable literature regarding reactive arthritis, especially publications that had a focus on urogenital triggers, with first and foremost *Chlamydia trachomatis*, were chosen when they discussed the typical inflammatory and clinical manifestations of the disease. During the process of writing this thesis, the selected literature was organized in four major themes: pathogenesis, clinical presentation, diagnosis, and treatment. By doing that, it was possible to synthesise current knowledge and newer knowledge as well as filtering established concepts and areas of ongoing uncertainty. All in all, the chosen study design intended to create a comprehensive, clinically oriented and academically grounded overview of arthritis associated with urogenital infection.

4.2. Data Sources and Search Strategy

For the thesis, a structured literature search was done mainly in PubMed, which was used as the main database, as it has a broad coverage of biomedical and clinical literature. Also, Google Scholar was used as a supplementary search tool to find additional and potentially relevant publications, especially review articles and papers that could not be found in a primary PubMed search. Furthermore, a manual screening of reference lists from relevant reviews and key articles was done to find more studies that were beneficiary. A specific author search was done to extract publications by Prof. I. Butrimienė, as specifically recommended by the thesis supervisor. The literature search was performed between April 2025 and March 2026. The strategy of search was based on multiple combinations of different relevant keywords which were related to the main topic of the thesis. The mandatory keyword “reactive arthritis” was included in all major searches. Additionally, terms like

“urogenital infection”, “*Chlamydia trachomatis*”, “pathogenesis”, “clinical presentation”, “diagnosis”, “treatment”, and “HLA-B27” were used. The process of the search in PubMed was done in a thematic manner, according to the contents of the major chapters of the thesis. When literature relevant to pathogenesis, clinical presentation, diagnosis or treatment was found, it was separated in specific folders to make sure that the review process was focused and organised. By using this approach, it was made sure to group and synthesise the evidence according to the main objectives of this thesis. Moreover, the search strategy focused on publications from the last 10 years, in accordance with the methodological recommendations of the Faculty of Medicine. However, older studies were also included if they represented landmark publications or could provide important foundational evidence, especially in the fields of immunopathogenesis, bacterial persistence, diagnostic concepts, and HLA-B27-associated mechanisms. All in all, the search strategy was designed to make sure that it was focused on the most important aspects but could also identify publications necessary for a comprehensive thesis, to ensure the inclusion of the most relevant literature on reactive arthritis associated with urogenital infections.

4.3. Inclusion and Exclusion Criteria

In this literature review, the selection process was based on the predefined relevance and methodological considerations. Usable publications were those which included reactive arthritis in the context of urogenital infection, with a strong focus on one or more of the main thematic areas of the thesis, hence pathogenesis, clinical presentation, diagnosis, and treatment. Preferably, publications from the last 10 years were used, as recommended in the methodological annex of the Faculty of Medicine. Sometimes, earlier studies were also included, but only if they represented landmark papers and provided important foundational evidence or were repeatedly cited in newer, relevant and guideline shaping reviews and therefore essential for understanding reactive arthritis, especially regarding *Chlamydia trachomatis*, bacterial persistence, immunopathogenesis, and HLA-B27-associated mechanisms. Different types of scientific publications were used, for example narrative reviews, systematic reviews, observational studies, clinical studies and mechanistic or translational studies, if they were relevant to the aim of the review. Publications by Prof. I. Butrimienė were specifically used and included where relevant, as requested by the supervisor. Many articles were excluded, especially if they did not specifically address reactive arthritis, were not relevant to the central topic of the thesis or mainly focused on unrelated arthritis conditions without a connection to infection associated mechanisms. Some case reports and isolated observations were used, but these were generally not prioritised and only used if they discussed a key clinical, diagnostic or therapeutic aspect. Publications with a major overlap with more high-quality sources, as well as papers for which full-text access was unavailable when essential for

interpretations, were excluded in most cases. All in all, these criteria made sure to have a focused and academically reliable selection of literature for the review.

4.4. Literature Selection and Synthesis

The selection of literature included several stages. An overview of the topic was conducted by reading landmark studies, relevant publications that are cited in international guidelines, as well as reading textbooks on the topic. Afterwards, potentially relevant publications were identified through search strings mentioned before on PubMed, including important keywords and combinations of those. When headings stroked attention through a matching approach of the topic, the publication was scanned through the abstract to clarify its relevance and if it matched predefined specifications. If they seemed relevant, they were stored in a specific Zotero folder to be further evaluated later in a full text form for detailed interpretation. During the final selection of sources, the above-mentioned publications were scanned for contribution to the thesis regarding research aim and usefulness for the thematic structure, their scientific relevance and clear structure to perfectly extract relevance for the thesis. Studies and reviews that provided clear evidence or a comprehensive discussion related to the four main domains were extracted and stored in another specific Zotero folder, which would be used later during the writing process. These studies were then further summarized and the key points, regarding to the specific topic that were proven or discussed, extracted and written down in a document linked to that specific publication. This ensured a smoother workflow during the writing process, as important aspects of each topic had at least one more publication to prove those. Where appropriate, recent and sometimes older reviews and well-known studies were included to ensure a combination of current perspectives with foundational evidence. The synthesisation of the publications followed a thematic approach, with the above-mentioned preselection by storing and summarising of a publication in one of the domain folders. Furthermore, within these broader folders another selection occurred when the publications were grouped regarding their relevance to subtopics within one broader domain. The selection of the subtopics occurred during the before mentioned overview gathering as well as simultaneously during the synthesization process within a broader domain. This allowed to integrate different types of publications as well as the possibility to compare different studies within a domain or even within a subtopic and shaped the thesis regarding the combination of current concepts, areas of agreement and discussion, as well as uncertainty's. Lithuanian publications, especially of Prof. I. Butrimienė were specifically analysed, as these provide regional relevance as well as profound additional perspectives on arthritis in the context of urogenital infection. Overall, the literature selection and synthesis process were designed to ensure a structured, critical, detailed and clinically meaningful review of the topic.

5. Pathogenesis

5.1. Infectious Triggers

Reactive arthritis is a sterile inflammatory arthropathy that typically develops after a mucosal infection, most commonly affecting the urogenital or gastrointestinal tract.(1,2) It belongs to the spectrum of spondyloarthritides and is characterised by an interval of days to weeks between the triggering infection and the onset of musculoskeletal symptoms.(1,2) Although the triggering infection itself may be asymptomatic or clinically mild, reactive arthritis represents a clinically relevant complication because of its ability for a prolonged disease course, extra-articular manifestations, and functional impairment.(2) When looking into a broader perspective and interpretation, reactive arthritis has also been discussed in relation to viral and other less common infection-related triggers, even though bacterial gastrointestinal and urogenital pathogens are still the best established classical causes.(2,7,8)

When considering urogenital pathogens, *Chlamydia trachomatis* is the best-established trigger of reactive arthritis and has been repeatedly implicated in both clinical cohorts and mechanistic studies.(2,4) The association between *C. trachomatis* infection and the following arthritis has led to the concept of “Chlamydia-induced reactive arthritis” as a prototypical form of infection-associated reactive arthritis.(2,4) In clinical practice, urogenital infection may present with dysuria, urethral discharge, cervicitis, or may remain subclinical; therefore, the absence of prominent urogenital symptoms does not exclude a causal infectious trigger.(4) This is of practical importance because delayed recognition of prior infection may lead to diagnostic delay and underestimation of infection-related arthritis.(4)

Prospective data provide important knowledge into the frequency with which reactive arthritis could develop after confirmed *C. trachomatis* infection. In a prospective analysis, 8.1% of followed patients developed symptoms compatible with Chlamydia-induced reactive arthritis within a short follow-up interval.(9) These observations are very informative as they reduce recall bias regarding preceding infection and strengthen the temporal relationship between exposure, as in urogenital infection and the outcome, as in arthritis.(9) In addition, they support the clinical rationale for actively assessing recent or recurrent urogenital symptoms, prior sexually transmitted infections, and potential exposure risks when evaluating patients with new-onset inflammatory arthritis, as the majority of patients who developed reactive arthritis after being tested positive for *C. trachomatis* were asymptomatic.(9)

Evidence from clinical series further supports the role of urogenital infections, especially *C. trachomatis*, as frequent triggers of reactive arthritis.(4) In cohorts describing potential triggering infections, urogenital inflammatory features and laboratory findings consistent with urogenital infection were common, and *C. trachomatis* was identified in the most cases.(4) These observations

are matching with the standard theory that urogenital infection represents a key initiating factor in a clinically relevant proportion of reactive arthritis patients.(4) Importantly, such cohorts also stress that reactive arthritis is often diagnosed in a context of imperfect microbiological confirmation, showing real-world limitations such as delayed testing, spontaneous pathogen clearance, or prior antibiotic exposure.(4) Nevertheless, the combination of clinical patterns, urogenital inflammatory signs, and pathogen detection supports the relevance of urogenital infections as triggers of reactive arthritis.(4,9)

While *C. trachomatis* represents the main urogenital trigger, the microbial spectrum which could be associated with reactive arthritis seems to be bigger and broader. Additional urogenital microorganisms, for example *Ureaplasma urealyticum* and *Mycoplasma hominis*, have been detected and suggested in reactive arthritis cohorts, but their pathogenetic significance is less consistent, as these organisms can also colonize the genitourinary tract without causing the disease.(3–6) Newer reviews stress that in addition to classical pathogens, a range of newly described, rare, or less frequently recognised infectious agents have been reported in association with reactive arthritis-like clinical presentations.(2) However, the strength of evidence varies heavily across pathogens, ranging from well-supported associations to isolated reports, and the clinical interpretation of these associations therefore must be handled with caution.(2) From a thesis perspective, this wider spectrum is relevant primarily to contextualise reactive arthritis as an infection-triggered condition rather than a disease linked to a single pathogen, while continuing to emphasise the best-evidenced urogenital trigger, *C. trachomatis*.(2)

An additional complexity arises when looking at polymicrobial involvement and co-infections. Reviews which discuss co-infection of *Chlamydiae* and other bacteria state that multiple pathogens may contribute to inflammatory processes in some patients.(10) This perspective is clinically reasonable because of the epidemiology of sexually transmitted infections and the possibility of simultaneous mucosal infections.(10) However, co-infection hypotheses should be interpreted critically, as the detection of microbial DNA or serological markers does not necessarily mean causality, and the clinical consequences for diagnosis and treatment are still incompletely defined.(10) For the purpose of this review, co-infection concepts point out ongoing uncertainties and research needs, while the primary narrative stays centred on the strongest and most consistent evidence base.(10)

Overall, urogenital infections represent a key triggering context for reactive arthritis, with *Chlamydia trachomatis* being the most strongly supported urogenital pathogen.(2,4,9) Prospective observations strengthen the timely association and indicate that a clinically meaningful proportion of patients may develop reactive arthritis-like symptoms after confirmed infection.(9) Clinical cohorts, including contributions from Lithuanian research, further support the relevance of

urogenital inflammatory features and *C. trachomatis* detection in reactive arthritis patients.(4) At the same time, broader microbial spectra and co-infection hypotheses highlight that infection-associated arthritis is a heterogeneous field in which causality and mechanisms may differ between patient subgroups.(2,10) These considerations provide an introduction to the following sections on pathogen persistence and immunopathogenic pathways.

5.2. Mechanisms of Bacterial Persistence

Reactive arthritis has traditionally been classified as a sterile inflammatory arthritis because viable microorganisms are usually not recovered from synovial fluid using standard microbiological culture techniques seen in clinical settings.(11) Despite this classification, a strong association with prior infections, particularly urogenital infection caused by *Chlamydia trachomatis*, has consistently been demonstrated.(11) This shaped the hypothesis that bacterial components or viable but non-cultivable organisms of the bacteria may persist in host tissues and play a role in the ongoing inflammatory responses within the joint.(11,12)

Increasing molecular evidence supports the concept that *C. trachomatis* can persist within synovial tissues after the initial mucosal infection has resolved.(12) Studies using polymerase chain reaction (PCR) techniques have detected chlamydial DNA in synovial tissue samples obtained from patients with reactive arthritis.(11) These outcomes suggest that bacterial material can be transported from the primary infection site to distant tissues, including the synovium.(12) One proposed mechanism is that infected monocytes or macrophages are acting as carriers that disseminate bacterial components through the bloodstream to the joint environment, where they may remain intracellularly within host cells.(11–14)

Importantly, several research literatures have shown that the detected bacterial material represents more than only residual DNA fragments which stem from non-viable organisms. Molecular analyses of synovial tissue have identified chlamydial ribosomal RNA (rRNA) and messenger RNA (mRNA), which are indicators of ongoing metabolic activity.(13,15) The detection of bacterial RNA transcripts suggests that the organisms present in synovial tissue remain biologically active instead of representing inactive residues of a previous infection.(13) In addition, studies have observed characteristic patterns of gene expression compatible with a persistent bacterial state.(13) For example, reduced expression of structural genes such as *omp1*, which encodes the major outer membrane protein (MOMP), has been reported alongside continued transcription of genes involved in stress response and intracellular survival.(13) This gene expression mechanism is consistent with a persistent, metabolically active but non-replicating bacterial form.

Another important observation supporting the persistence hypothesis is that chlamydial nucleic acids can sometimes still be detected in synovial tissue even after prolonged antibiotic

treatment.(16) Clinical studies examining synovial biopsies from patients with chronic reactive arthritis have demonstrated that, despite negative bacterial cultures and negative direct fluorescent antibody tests, synovial tissue may remain positive for chlamydial DNA or RNA when analysed using sensitive molecular techniques such as PCR or in situ hybridisation.(16,17) The results indicate that persistent chlamydial organisms may evade both routine microbiological detection and antimicrobial therapy.(16) Therefore, the persistence of bacterial components within synovial tissue may contribute to the chronic or relapsing nature of reactive arthritis observed in some patients.(16) The biological basis for this phenomenon stems from the unique developmental cycle of *C. trachomatis*. In normal conditions, the bacterium can switch between infectious elementary bodies and metabolically active reticulate bodies within a host cell. However, under conditions of cellular stress, for example, the exposure to interferon- γ , nutrient deprivation, or certain antimicrobial agents, the normal developmental cycle can be disrupted.(12) In response to such stressors, *Chlamydiae* may enter a persistent state defined by enlarged aberrant reticulate bodies, reduced replication, and markedly decreased production of infectious elementary bodies.(12) Even though in this state the replication is limited, the bacteria remain metabolically active and can keep the ability to continue normal growth when better conditions return.(12) This reversible persistence strategy allows the organism to survive within host cells for extended periods and may explain why complete eradication of the pathogen from synovial tissues can be difficult to achieve.(12) Another way in which *C. trachomatis* is able to ensure a persistence state is its survival in host cells, as it can inhibit the fusion of phagosomes and lysosomes intracellularly, thus making it possible to survive.(1)

Persistent intracellular infection may also influence host inflammatory pathways. Experimental studies using primary human synovial cells have shown that *C. trachomatis* can infect synovial cells and modulate host immune signalling pathways involved in inflammation.(18) For example, modulation of inflammasome-associated signalling and cytokine responses has been observed following infection of synovial cells with *C. trachomatis*.(18) These interactions between persistent intracellular bacteria and host immune mechanisms could contribute to the sustained inflammatory responses observed in reactive arthritis.(18)

All in all, current evidence supports the concept that bacterial persistence represents a key link between the initial urogenital infection and the development of reactive arthritis.(11,12,15) The presence of metabolically active chlamydial organisms or bacterial components within synovial tissues may provide a continuous stimulus for immune activation even in the absence of detectable active infection.(12,15) These findings highlight the complicated interplay between microbial persistence and host immune responses, which ultimately contributes to the chronic or recurrent nature of reactive arthritis.

5.3. Immunological Mechanisms

Reactive arthritis develops as a consequence of the complex dynamic between persistent microbial stimuli and the host immune system. While bacterial persistence provides the initial trigger, the development and maintenance of synovial inflammation are largely driven by dysregulated immune responses. Current evidence supports a model in which innate immune activation to persistent bacterial remnants and antigens, adaptive immune polarisation, cytokine-mediated amplification with a potential autoimmune mechanism, interact to sustain joint inflammation in reactive arthritis.(1,14,17)

The innate immune system takes up a key role in translating persistent bacterial signals into inflammatory responses. When looking at Chlamydia-induced reactive arthritis, bacterial components such as lipopolysaccharide (LPS), DNA, and other pathogen-associated molecular patterns (PAMPs) can be detected within the joint and will serve as continuing stimuli for immune activation. These components are recognized by pattern recognition receptors, including Toll-like receptors (TLRs), expressed on innate immune cells such as monocytes, macrophages, and dendritic cells.(1,14,17) Activation of these receptors initiates intracellular signalling cascades leading to the production of proinflammatory cytokines, including tumor necrosis factor alpha (TNF- α), interleukin-1 (IL-1), and interleukin-6 (IL-6).(17) These cytokines contribute to endothelial activation, leukocyte recruitment, and synovial inflammation. In addition, monocytes and macrophages may play a dual role in reactive arthritis, acting both as carriers of persistent bacterial components and as effector cells that increase local inflammation.(14,17) The continued presence of bacterial antigens in synovial tissue makes sure that innate immune activation is not a transient event but may persist over time, causing chronic inflammation.(15)

Following innate immune activation, adaptive immune responses play a role in the persistence and progression of synovial inflammation. In particular, T-cell-mediated immunity plays a central role in reactive arthritis.(1,17)

The immune response to intracellular pathogens such as *Chlamydia trachomatis* would normally involve a strong T helper 1 (Th1) response characterized by the production of interferon-gamma (IFN- γ), which is essential for bacterial clearance. However, in reactive arthritis, this response appears to be insufficient, allowing bacterial persistence.(17)

At the same time, evidence suggests that proinflammatory T-cell responses remain active within the joint. Studies have demonstrated the presence of T cells producing IFN- γ in synovial fluid and tissue, which shows ongoing immune activation.(19) In addition to Th1 responses, T helper 17 (Th17) cells have appeared as major contributors to inflammation in reactive arthritis and related spondyloarthritides.(20,21) Th17 cells produce interleukin-17 (IL-17), a cytokine with potent

proinflammatory effects that promotes neutrophil recruitment and activation of synovial cells.(20–22) The combination of Th1- and Th17-associated responses leads to the assumption that reactive arthritis is defined by a complex and dynamic immune environment rather than a single dominant pathway.(1,20,21)

Another important mechanism in the pathogenesis of reactive arthritis are Cytokines, as they represent a key mediator which link immune activation to sustained synovial inflammation. Among these, TNF- α plays a central role as a master regulator of inflammation. It is produced by activated macrophages and other immune cells in response to persistent bacterial stimuli and contributes to the amplification of inflammatory pathways within the joint.(1,17) The clinical relevance of TNF- α is shown in the therapeutic use of TNF inhibitors in patients with chronic or refractory reactive arthritis.(1)

The interleukin-23/interleukin-17 (IL-23/IL-17) axis is an additional critical pathway in the immunopathogenesis of reactive arthritis.(20) IL-23 promotes the expansion and maintenance of Th17 cells, while IL-17 acts on various cell types, including synovial fibroblasts, macrophages and endothelial cells, to induce the production of additional cytokines and chemokines.(20,22) These include IL-6 and chemokines such as IL-8, which promote the recruitment of neutrophils and therefore amplify inflammation.(20,22)

This cytokine network creates a self-sustaining inflammatory loop in which persistent antigenic stimulation leads to a continuing cytokine production, immune cell recruitment, and synovial activation. Even when bacterial load decreases, the continuation of cytokine signalling may maintain inflammation, explaining the chronic or relapsing course observed in some patients with reactive arthritis.(1,15)

The transition from infection-driven inflammation to a more autonomous, immune-mediated disease process remains an important aspect of reactive arthritis pathogenesis. Several mechanisms have been proposed to explain this transition, including molecular mimicry and HLA-B27-associated immune responses.(1,17)

Molecular mimicry refers to the structural similarity between bacterial antigens and host proteins, which may result in cross-reactive immune responses that target host tissues.(17)

In addition, HLA-B27 is strongly associated with reactive arthritis and may affect disease susceptibility and progression through multiple mechanisms, including modified antigen presentation, misfolding of the molecule, and modulation of immune signalling pathways.(17)

These processes may play a role in the persistence of inflammation even in the absence of active infection. Importantly, infection and autoimmunity should not be viewed as mutually exclusive mechanisms in reactive arthritis. Rather, persistent bacterial components may initiate and sustain

immune activation, while autoimmune-like processes may contribute to disease chronicity and progression.(1,14,17)

Taken together, current evidence supports an integrated model in which microbial persistence and dysregulated immune responses together drive the pathogenesis of reactive arthritis.

5.4. Role of HLA-B27

Human leukocyte antigen B27 (HLA-B27) is one of the most important genetic factors associated with the development of reactive arthritis and other spondyloarthritides.(23,24)

A strong association between HLA-B27 positivity and reactive arthritis has been repeatedly demonstrated, with a significantly higher prevalence of HLA-B27 when looking at affected patients compared to the general population.(23,24) In addition, HLA-B27-positive individuals are more likely to develop more severe disease manifestations, including prolonged disease duration, axial involvement, and an increased risk for chronic or recurrent arthritis.(23,24)

Clinical studies have also highlighted the differences between HLA-B27-positive and HLA-B27-negative patients. HLA-B27 positive patients have been associated with a higher frequency of axial involvement, whereas HLA-B27-negative reactive arthritis can show more involvement of peripheral joints, including the upper extremities and small joints. Although these differences in clinical phenotype, the overall severity of systemic inflammation seen in laboratory findings may be comparable between groups. These results show that HLA-B27 not only plays a part to disease susceptibility but also determines the disease phenotype and is a predictive factor for progression.(23) Several mechanisms have been mentioned in the literature to explain the specific role of HLA-B27 in the pathogenesis of reactive arthritis. One of the most discussed hypotheses is the arthritogenic peptide theory, which suggests that HLA-B27 presents bacterial peptides that mimic host antigens, leading to a cross-reactive T-cell response. In addition, HLA-B27 has a tendency to misfold within the endoplasmic reticulum, which may induce cellular stress responses and promote proinflammatory signalling pathways. Furthermore, the formation of unusual HLA-B27 structures, including homodimers and heterodimers, has been suggested to alter immune cell interactions as well as contribute to dysregulated immune responses.(17)

Despite the strong association between HLA-B27 and reactive arthritis, the presence of this genetic factor alone is not sufficient to cause disease. Many HLA-B27-positive individuals never develop reactive arthritis, while some patients without HLA-B27 still develop the condition. This indicates that reactive arthritis is a multifactorial disease in which genetic predisposition interacts with environmental triggers, particularly infection, and host immune responses. In this context, HLA-B27 may act as a modifier of disease susceptibility and severity instead of a direct cause of disease.(1)

Overall, HLA-B27 plays a central role in directing both susceptibility to and the clinical course of reactive arthritis. Its interaction with persistent bacterial components and the host immune system provides an important link between infection, immune dysregulation, and chronic inflammation. Knowing these mechanisms is necessary to understand disease heterogeneity and may also have consequences for prognosis and therapeutic decision-making.(1)

5.5. From Acute to Chronic Disease

Reactive arthritis typically has an acute course, with symptoms developing within days to weeks after a triggering infection and resolving within 6–12 months in many patients.(1) However, the disease course is highly variable, and a substantial proportion of patients develop chronic reactive arthritis lasting more than 6 months and requiring re-treatment; in some cases, patients evolve toward other spondyloarthritis phenotypes (e.g., ankylosing spondylitis or inflammatory bowel disease–associated manifestations).(1)

One of the key determinants of chronic disease is the persistence of bacterial components within host tissues. Chlamydia species can enter a long-lasting “persistence” program that is described as a viable but non-cultivable state,(12) and in chronic Chlamydia-induced reactive arthritis, the organism can be present and metabolically active in synovial tissue even during clinically remitting phases.(15) One possible mechanism for this persistence could be explained by *Chlamydia trachomatis* capability to hinder the combination of phagosomes and lysosomes intracellularly(25). Even when bacterial load in synovial tissue is lower in remitting than in active disease, pro-inflammatory transcripts can be equal to or higher than those in active disease, supporting the concept that reduced bacterial burden may still maintain immune activation and contribute to remitting–relapsing disease patterns.(15)

In addition to microbial persistence, dysregulation of the immune response plays a central role in the transition from acute to chronic disease. A recent review summarized the stage-dependent cytokine patterns in reactive arthritis and reported that the acute disease can show relatively low IFN- γ and TNF- α with higher IL-10 in synovial fluid, whereas TNF- α may be elevated in chronic reactive arthritis which is consistent with persistent synovial inflammation.(1) Furthermore, IL-17/IL-23–associated pathways are implicated in reactive arthritis, as IL-17 has been detected in synovial fluid and bacterial antigens can stimulate synovial immune cells to produce IL-17 and IL-23 (1); in the larger spondyloarthritis literature, accumulated genetic, experimental, and clinical evidence supports a clear pathogenic role for the IL-17 pathway.(20) When persistent antigenic stimulation and amplified cytokine signalling work together, particularly TNF- α and IL-17-related networks, they provide a reasonable basis for a self-perpetuating inflammatory environment that could lead to difficulties regarding the spontaneous resolution.(1,20)

Genetic factors additionally contribute to disease phenotype and progression, with HLA-B27 representing a key genetic background in reactive arthritis within the spondyloarthritis spectrum.(23) In a retrospective cohort, HLA-B27-positive patients showed a higher likelihood of axial involvement and more axial symptoms compared with HLA-B27-negative patients.(23) Consistently, another study finds that HLA-B27 is linked to a more severe arthritis development, particularly sacroiliitis and enthesitis, and may suggest an evolution of reactive arthritis toward ankylosing spondylitis.(24)

Additional factors influencing disease course include characteristics of the triggering infection, host immune regulation, and environmental or microbiome-related influences. A contemporary review frames reactive arthritis as a dynamic interface between environmental triggers and genetic susceptibility and highlights infection history (etiological agents), cytokine responses, genetic factors (including HLA-B27), and gut microbiota as major contributors to disease development and variability.(1) The same review notes that reactive arthritis typically occurs sporadically but may occur with increased frequency in the setting of infection outbreaks, pointing out the importance of exposure context and pathogen dynamics.(1)

Taken together, the transition from acute to chronic reactive arthritis shows a multifactorial process in which persistent microbial stimuli, dysregulated immune responses, and genetic predisposition interact to sustain inflammation.(1,12,15,20) Knowing these mechanisms is important for identifying patients at risk for chronic disease and for developing specific therapeutic strategies which are directed to the interruption of key inflammatory pathways, including TNF- α and IL-17-related networks, to prevent these patients from developing chronic destructive arthritis.(1,20)

6. Clinical Presentation

6.1. Overview and Typical Clinical Features

Reactive arthritis is an inflammatory joint disease that typically develops after a preceding infection, most commonly of the urogenital or gastrointestinal tract.(1) The onset of arthritis is generally within days to weeks after enteritis or urethritis (reported diagnostic/classification time window: 3 days to 6 weeks) and is characterised by mostly asymmetric mono- or oligoarthritis with especially lower-limb involvement.(1) The clinical presentation can vary considerably between patients, ranging from mild, self-limiting symptoms to more severe and prolonged disease courses.(1) Recent reviews also emphasise an expanding spectrum of implicated infectious triggers beyond the classic pathogens, supporting clinical heterogeneity across patients.(2)

The most characteristic feature of reactive arthritis is an acute asymmetric oligoarthritis, typically peripheral and predominantly affecting the lower extremities.(1) Large joints (especially the knee, followed by ankle/talocrural and foot joints) are commonly involved, and some cohorts report an average of 5 regarding tender joint count among reactive arthritis subjects in clinical series.(1)

Other cardinal symptoms involve Extra-articular manifestations and contribute substantially to the clinical picture, consistent with reactive arthritis as part of the spondyloarthritis spectrum.(1)

Review data show many patients with genitourinary symptoms such as urethritis, cervicitis, cystitis, prostatitis, patients with ocular involvement such as conjunctivitis in acute disease and uveitis more often reported in chronic disease, and mucocutaneous findings, including keratoderma blennorrhagicum and circinate balanitis, with approximate frequencies in 10-40%.(1) Those systemic features support the classification of reactive arthritis within the wider spondyloarthritides and help differentiate the syndrome from other inflammatory arthritis syndromes when combined with a compatible post-infectious history.(1)

Enthesitis is a frequent accompanying symptom; it has been suggested to be common (and in chronic Chlamydia-induced reactive arthritis reported in the 30–60% range), with Achilles enthesitis specifically documented.(1) Another accompanying symptom may be dactylitis, diffuse swelling of an entire digit (“sausage digit”), which represents a less common but characteristic feature associated can be observed in up to 40% of patients.(11)

Axial involvement as an accompanying symptom can occur in a subset of patients and may include inflammatory back pain and/or sacroiliitis, overlapping clinically with other spondyloarthritis phenotypes.(1) In a retrospective reactive arthritis cohort, HLA-B27–positive patients showed more axial symptoms than HLA-B27–negative patients, supporting HLA-B27 as a contributor to phenotype differences.(23) In addition, radiographic sacroiliitis is reported in chronic reactive arthritis cohorts summarised in the main review, aligning axial manifestations with a more spondyloarthritis-like disease course and potential chronicity signals in selected patients.(1)

The clinical course of reactive arthritis is variable: the course can differ in duration and relapse/severity patterns throughout patients.(1) In the main review synthesis, most patients are described as reaching complete remission within 6–12 months, while 30–63% may develop chronic disease lasting beyond 6 months and requiring re-treatment; some patients develop features consistent with ankylosing spondylitis or inflammatory bowel disease over time.(1) Factors summarised as causing a worse prognosis include HLA-B27 positivity, Chlamydia-induced infection, spondyloarthritis family history, and chronic bowel inflammation, stressing the importance of early recognition and suitable management to reduce long-term complications.(1,23)

6.2. Articular Manifestations

Articular involvement represents the core clinical feature of reactive arthritis and is usually characterised by an acute onset of asymmetric oligoarthritis predominantly affecting the lower extremities.(26) The arthritis usually develops within one to three weeks following a preceding infection, however in patients with *Chlamydia trachomatis* a longer latency period is observed in about one third of patients, leading to silent infections as clinical manifestations can occur after 4 weeks, especially in females.(26) Any peripheral joint could be infected but most involved are large joints such as the knees, which were involved in 64.7% of female patients and 52.12 % of male patients, the talocrural joint in about 50% of female and 57% of male patients, the metatarsophalangeal joint with involvement in about 46% of patients as well as the radiocarpal joint in about 46% of patients.(1) Although the lower limbs are preferentially affected, upper extremity involvement may occur in milder HLA-B27 negative cases, particularly involving smaller joints.(23,26)

The pattern of joint involvement in reactive arthritis is typically asymmetric and oligoarticular, manifested in 70% of female patients and 73% of male patients, separating it from other inflammatory arthritides such as rheumatoid arthritis, which more commonly presents with symmetric polyarthritis.(1,27) Patients frequently report acute joint pain, swelling, and stiffness, often associated with functional impairment.(1,2,26) The inflammatory nature of reactive arthritis and its matching symptoms mentioned above is consistent with its classification within the spondyloarthritis spectrum.(1,26)

A characteristic feature of reactive arthritis within the spondyloarthritis spectrum is the involvement of enthesitis, the sites where tendons and ligaments insert into bone. Enthesitis is commonly observed in most cases at the Achilles tendon, also at the plantar fascia, quadriceps tendon, or patellar tendon and typically presents with localized pain, swelling, heat sensation and tenderness, possibly resulting in impaired mobility.(7) The presence of enthesitis furthermore supports the

classification of reactive arthritis within the spondyloarthritis group and represents an important clinical feature in the diagnostic assessment and may help differentiate it from other joint diseases.(1,7)

Dactylitis, often referred to as “sausage digit,” is another important clinical manifestation and is characterized by diffuse swelling of an entire finger or toe.(7) It results from a combination of synovitis, tenosynovitis, and soft tissue inflammation and is considered a hallmark feature of spondyloarthritis.(26) Although not present in all patients, its occurrence strongly supports the diagnosis of reactive arthritis in the appropriate clinical context.(1,7)

In addition to joint and enthesal involvement, periarticular structures may also be affected. Bursitis and tenosynovitis can contribute to pain and functional limitation and may increase the complexity of the clinical picture.(26) These manifestations highlight that reactive arthritis is not limited to the synovial membrane but involves multiple components of the musculoskeletal system.

The severity of articular involvement may vary widely between patients. Whilst some individuals experience milder and self-limiting symptoms, others can develop more severe inflammation which affects multiple joints and causes significant impairment.(1) In some cases, articular symptoms may persist or recur over time, helping to drive towards chronic disease progression.(1)

Overall, the articular manifestations of reactive arthritis are characterised by a combination of asymmetric oligoarthritis, enthesitis, and dactylitis, mainly affecting the lower extremities. These features, together with the temporal relationship to a preceding infection, form the basis of clinical diagnosis and provide important clues for differentiating reactive arthritis from other inflammatory joint disorders.(1,2,23,26)

6.3. Axial Involvement

Axial involvement in reactive arthritis occurs less frequently than peripheral joint manifestations but represents an important aspect of the disease spectrum.(1) It typically presents as inflammatory back pain, which is characterised by insidious onset, worsening during rest, and nocturnal pain that may awaken patients during the second half of the night.(26) Pain often radiates to the buttocks, reflecting involvement of the sacroiliac joints.(26)

Sacroiliitis is the most common form of axial involvement in reactive arthritis seen in approximately 20% of patients and may be detected clinically or with imaging studies.(7) In the early stages, sacroiliac joint inflammation may not be evident on conventional radiographs, even though magnetic resonance imaging (MRI) can reveal active inflammatory changes such as syndesmophytes.(28) Although axial involvement is generally less prominent than in ankylosing spondylitis, its presence suggests a closer relationship to the wider spectrum of spondyloarthritides.(1,24)

Axial manifestations are more frequently observed in patients who are positive for HLA-B27, and this genetic factor has been associated with an increased risk of sacroiliitis, a persistent disease course and progression to chronic disease. Patients with axial involvement often experience a more persistent disease course and may develop features overlapping with other forms of spondyloarthritis, including ankylosing spondylitis.(24)

The clinical recognition of axial involvement is important, as it may affect both diagnostic classification and management strategies. Inflammatory back pain in the context of a recent infection and peripheral arthritis may raise suspicion for reactive arthritis, particularly in HLA-B27-positive individuals. Early identification of axial disease may also be relevant for monitoring disease progression and guiding therapeutic decisions.

6.4. Extra-articular Manifestations

Extra-articular manifestations are a common and clinically important feature of reactive arthritis, showing the systemic nature of the disease. These manifestations can involve the urogenital tract, eyes, skin, and less frequently other organ systems. In many cases, extra-articular symptoms may show up before, whilst, or after the actual onset of joint inflammation and can play a very important role to the overall disease severity.

Urogenital manifestations are often the initial presentation in patients with reactive arthritis triggered by urogenital infection. Symptoms may include urethritis, characterised by dysuria and urinary frequency, as well as cervicitis in women. In some cases, additional complications such as prostatitis, salpingitis, or vulvovaginitis may occur. However, urogenital infections are frequently asymptomatic, particularly in women, which is able to complicate the identification of the triggering event. Despite this, the presence of urogenital symptoms in combination with arthritis should raise suspicion for reactive arthritis.(1,26)

Ocular involvement is one of the most frequent extra-articular manifestations and may occur early in the disease course with sometimes an intermitted pattern. Conjunctivitis is the most common presentation and is mostly mild and transient, whereas anterior uveitis represents a more severe form that may be recurrent and associated with pain, redness, and visual impairment in the form of blurred vision. Ocular manifestations can occur in a significant proportion of patients and are important to recognise due to the potential risk of complications if left untreated.(1,26)

Cutaneous manifestations are characteristic but less common features of reactive arthritis.

Keratoderma blennorrhagicum presents as hyperkeratotic skin lesions, most commonly affecting the soles of the feet and, less frequently, the palms. Another distinctive manifestation is circinate balanitis, which presents as painless, superficial lesions on the glans penis. Oral ulcers may also

occur but are often transient and asymptomatic. Although these dermatological features are not present in all patients, they are highly suggestive of reactive arthritis when observed in the appropriate clinical context.(1,26)

Less commonly, reactive arthritis may involve other organ systems. Cardiac manifestations, including conduction abnormalities, aortic regurgitation, and pericarditis, have been reported, particularly in patients with prolonged disease. Although rare, these complications highlight the systemic nature of the disease and point out the value of a comprehensive clinical assessment in affected patients to minimize complications.(1,26)

All in all, extra-articular manifestations represent an essential and important component of the clinical presentation of reactive arthritis. Their recognition is crucial for the accurate diagnosis of reactive arthritis, as the combination of articular and extra-articular features, especially in the context of a possible preceding infection, shows important diagnostic hints. Furthermore, these manifestations may affect the disease severity, prognosis, and management strategies.

6.5. Clinical Course and Disease Patterns

Reactive arthritis can follow many different paths. For some people, symptoms go away within three to six months after the first episode. Others may continue to have symptoms, experience relapses, or develop chronic inflammatory arthritis. This shows how varied the disease can be.(1)

Acute reactive arthritis is, as stated before, usually characterised by a sudden onset of asymmetric oligoarthritis, often accompanied by extra-articular manifestations. During this phase, symptoms are often at their worst and can limit physical activity. In many cases, inflammation gradually goes away without lasting effects. However, symptoms can return, especially if there is a new or ongoing infection.(1,26) Chronic reactive arthritis is generally defined by the persistence of symptoms beyond six months. In these patients, inflammation may occur in a varying pattern, with periods of remission and exacerbation. Chronic disease may involve both peripheral joints and axial structures and is more often associated with functional impairment and reduced quality of life. The transition from acute to chronic disease demonstrates the complexity of the interaction between persistent microbial factors and sustained immune activation.(1,15)

Different factors have been associated with an increased risk of a chronic or severe disease. HLA-B27 positivity is one of the most important predictors and has been linked to a prolonged disease duration, axial involvement, and a higher likelihood of recurrence.(23,24) In addition, persistent infection, particularly with *Chlamydia trachomatis*, could result in ongoing immune stimulation and chronic inflammation.(15) A more severe initial presentation and delayed or inadequate treatment of the triggering infection may similarly affect disease progression.(1)

Recurrent reactive arthritis represents another important disease pattern. Some patients experience repeated episodes of arthritis, which could be triggered by a reinfection or reactivation of persistent bacterial components in the body. These recurrent forms can sometimes lead to a chronic disease pattern, especially in genetically predisposed individuals. The difference between recurrent and chronic disease is not always clear, as both patterns may overlap in clinical practice.(1) Overall, the clinical course of reactive arthritis can show a changing and multifactorial process. While many patients experience complete recovery, a considerable number of patients develop chronic or recurrent disease requiring long-term management. Recognition of disease patterns and associated risk factors is essential for prognostic assessment and may help when making clinical decisions.

6.6. Laboratory and Clinical Findings

Laboratory and clinical findings in reactive arthritis are mostly nonspecific but can contribute to the clinical assessment in general by showing systemic inflammation, evidence of preceding infection, and features characteristic of the spondyloarthritis spectrum.

Markers of systemic inflammation, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) tend to be elevated during the acute phase of reactive arthritis. However, their levels may vary considerably between patients and do not consistently correlate with disease activity. In some cases, especially in milder disease, inflammatory markers can remain within normal ranges despite active clinical symptoms.(1)

When analysing synovial fluid, in many cases inflammatory characteristics can be seen, such as elevated leukocyte counts with a predominance of neutrophils. What is important to note is that synovial fluid cultures are negative, which shows the non-purulent and “sterile” nature of reactive arthritis, even with its association with a preceding infection. This feature is especially important whilst differentiating reactive arthritis from septic arthritis and other infectious joint diseases.(1,26)

Evidence of a preceding infection represents a key component of the clinical picture. In patients with urogenital reactive arthritis, signs of *Chlamydia trachomatis* infection may be present, even though such infections are frequently asymptomatic, especially in women. In cases of enteric infection, microbiological or serological evidence may be identified but the causative pathogen is not always recognizable at the time of arthritis onset.(26)

Genetic predisposition additionally helps in completing the clinical profile of reactive arthritis. HLA-B27 positivity is often observed and is associated with an increased risk of disease development, as well as a higher likelihood of severe or prolonged disease and axial involvement.(23,24) Therefore, HLA-B27 status represents an important clinical feature in the overall assessment. Imaging findings are often without any trace of disease in the early stages of

reactive arthritis but can sometimes indicate characteristic changes in more advanced or persistent disease. Conventional radiography may demonstrate suspicious features such as joint space narrowing or sacroiliitis in chronic cases. Magnetic resonance imaging (MRI) is more sensitive for detecting early inflammatory changes, particularly in the sacroiliac joints, while ultrasound may identify synovitis, enthesitis, and tenosynovitis.(1)

All in all, laboratory and imaging findings support the overall clinical assessment of reactive arthritis by giving evidence of inflammation, a prior infection, and characteristic musculoskeletal involvement. However, no single finding is absolute, and the diagnosis still remains mostly on clinical evaluation in the appropriate context.

7. Diagnosis

7.1. Diagnostic Approach and Overview

The diagnosis of reactive arthritis is primarily clinical and is based on the combination of a preceding infection and characteristic musculoskeletal and extra-articular manifestations as well as ruling out other causes of arthritis. There are no universally accepted diagnostic criteria specifically for reactive arthritis, and diagnosis therefore relies largely on clinical assessment. A careful evaluation of patient history, symptom onset, and pattern of joint involvement is therefore fundamental. A key element in the diagnostic approach is the identification of a triggering infection, most commonly involving the urogenital or gastrointestinal tract. The onset of arthritis typically occurs within one to four weeks after the initial infection, although this interval may vary. In some cases, especially in urogenital infections caused by *Chlamydia trachomatis*, the preceding infection can be asymptomatic, which can complicate the diagnosis of the disease.(1,26)

As mentioned above the clinical presentation of reactive arthritis is characterised by asymmetric oligoarthritis, predominantly affecting the lower extremities, often accompanied by enthesitis, dactylitis, and extra-articular manifestations such as conjunctivitis or urethritis. The combination of these features, together with a temporal relationship to infection, will support the diagnosis in the matching clinical context.(1)

Laboratory and imaging findings can help in the diagnostic process. Markers of inflammation, such as CRP and ESR, can sometimes be elevated, however they are nonspecific. Similarly, detection of HLA-B27 may support the diagnosis but is not definitive. Identification of the triggering pathogen through microbiological testing such as a urethral swab, can be helpful but is not always possible, especially when the infection has resolved by the time arthritis develops.(1,26)

An important aspect of the diagnostic approach is ruling out alternative diagnoses, first and foremost septic arthritis, which requires urgent treatment. Synovial fluid analysis may therefore be essential, particularly in patients presenting with acute monoarthritis or severe joint inflammation. The absence of detectable pathogens in synovial fluid, together with the clinical context, supports the diagnosis of reactive arthritis.(7,26)

All in all, the diagnosis of reactive arthritis primarily depends on the overall combination of clinical features, supportive laboratory findings, and exclusion of other conditions. As there is no specific diagnostic criterion, a structured and comprehensive approach is needed to make sure an accurate and timely diagnosis is done.

7.2. Clinical Diagnostic Criteria

In contrast to many other rheumatic diseases, reactive arthritis does not have a universally accepted or validated diagnostic criteria. With reactive arthritis, the diagnosis is based on a combination of

clinical features, a history of preceding infection, and supportive laboratory findings. Therefore, the concept of “clinical diagnostic criteria” in reactive arthritis depends more to a characteristic pattern of disease rather than a normed, standardised classification system.

Different sets of proposed diagnostic criteria have been previously described in the literature. Most of the times they include major criteria, including the presence of asymmetric oligoarthritis predominantly affecting the lower extremities and a preceding symptomatic infection, as well as minor criteria, including evidence of a triggering pathogen or characteristic extra-articular manifestations, which were discussed above. A “definite” diagnosis has been suggested when both major criteria and at least one relevant minor criterion is fulfilled, and a “probable” diagnosis should be considered when only part of these criteria are present, in the sense of both major criteria, or one major and one minor criterion fulfilled.(1,26) However, these criteria have not been universally validated and are not routinely or internationally applied in clinical practice.

An important element in the clinical assessment regarding the proper diagnosis is the identification of a preceding infection, most commonly involving the urogenital or gastrointestinal tract. The temporal relationship between infection and the onset of arthritis is particularly important, with symptoms typically developing within one to four weeks. Nevertheless, this association may not always be evident or possible, especially because of cases of asymptomatic urogenital infection, which can complicate the diagnostic process.(1,26)

If a patient presents with asymmetric oligoarthritis predominantly affecting the lower extremities it should be viewed as a key diagnostic feature regarding the diagnosis of reactive arthritis. Additional musculoskeletal features such as enthesitis and dactylitis further support the diagnosis and help distinguish reactive arthritis from other inflammatory joint diseases. The presence of these features within the broader spectrum of spondyloarthritis represents an important diagnostic clue.(1)

If additionally, to the above mentioned asymmetric oligoarthritis, the patient also presents with extra-articular manifestations, it increases the likelihood of the correct clinical diagnosis. The combination of arthritis with urogenital symptoms, ocular involvement (such as conjunctivitis or uveitis), and mucocutaneous lesions is highly suggestive of reactive arthritis. Although the classic triad of arthritis, urethritis, and conjunctivitis (can’t see, can’t pee, can’t climb a tree is mentioned in many clinical guidelines) is well known, it is not present in all patients, and only looking for this triad can lead to underdiagnosis.(26,29)

In clinical practice, classification criteria developed for spondyloarthritis, such as those of the Assessment of SpondyloArthritis International Society (ASAS), may support the diagnostic process, particularly in patients with axial or peripheral manifestations. However, these criteria are not specific for reactive arthritis and should be applied with caution in this context.(30)

All in all, the clinical diagnosis of reactive arthritis works by recognising a characteristic constellation of multiple findings, including a preceding infection, asymmetric oligoarthritis, typical extra-articular manifestations, and features that are consistent with spondyloarthritis. As the before mentioned absence of definitive diagnostic criteria, clinical expertise and careful assessment are the most essential parts for accurate diagnosis regarding the clinical diagnostic criteria.

7.3. Laboratory Diagnostics

Laboratory diagnostics in reactive arthritis are mainly used to support the clinical diagnosis, identify a preceding infection, and to exclude any alternative conditions. There isn't a laboratory test which definitely confirms the diagnosis for reactive arthritis, and findings are generally nonspecific. However, a combination of inflammatory markers, microbiological testing, and genetic factors can give important diagnostic help.

Markers of systemic inflammation, including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), are frequently elevated during the acute phase of reactive arthritis. These markers reflect ongoing inflammatory activity but lack specificity and may be normal in some patients, particularly in milder cases or during later stages of the disease, or sometimes highly elevated in other differential diagnoses. Therefore, they should be interpreted in the context of clinical findings.(1,26)

Microbiological testing may contribute to the identification of the triggering infection. In cases of suspected urogenital reactive arthritis, nucleic acid amplification tests (NAATs) are the preferred method for detecting *Chlamydia trachomatis*, using first void urine samples or urethral and cervical swabs, due to their high sensitivity and specificity.(1) Compared to conventional culture methods, molecular techniques are more sensitive and have largely replaced culture-based diagnostics in clinical practice.(30) However, the pathogen that caused the reactive arthritis is often no longer detectable at the time of arthritis symptom onset, which limits the diagnostic yield of these tests.(1,26)

The detection of *Chlamydia trachomatis* can be diagnostically more complex in women, as the infection is often asymptomatic, and the sensitivity of detection depends on the sampling site. Earlier studies of Domeika and colleagues, including work with Prof. I. Butrimienė, showed polymerase chain reaction-based detection from self-collected vaginal or introital specimens is possible and diagnostically useful, especially as a less invasive and more easily accessible alternative to cervical sampling. Guideline literature that followed also supported nucleic acid amplification testing on self-taken vaginal samples as a legitimate diagnostic approach in women. In the context of reactive arthritis, these findings are especially relevant as they show the

importance of appropriate sampling strategies when a urogenital trigger is suspected but clinically undetected or hidden.(31–33)

Serological testing for *C. trachomatis* antibodies could sometimes be used in special cases, particularly when direct pathogen detection is not possible. However, serology has limited specificity as there is a high prevalence of antibodies in the population, as well as possible cross-reactions to other Chlamydia strains. Because of this, serology may not be able to differentiate between past and present infection.(26) Furthermore, in most cases, there is a delay of several days regarding the test results, which is an additional limiting factor regarding the diagnostics.(1) Another downside is that there is a delay in antibody production following antigen exposure. However, in the context of postinfectious complications such as reactive arthritis, serological markers—including IgA, IgM, and IgG antibodies—may provide indirect evidence of prior or persistent infection.(30) As a result, it is generally considered less useful than molecular diagnostic methods in the evaluation of reactive arthritis.(1)

Genetic testing for HLA-B27 is frequently included in the diagnostic workup. Although not specific for reactive arthritis, HLA-B27 positivity supports the diagnosis in the appropriate clinical context and is associated with a higher risk of severe or chronic disease. Its presence may also be helpful in patients with atypical presentations or when axial involvement is suspected and can help filter patients at risk of a more prolonged or extreme disease course.(23,24)

Additional laboratory tests may be performed to exclude other causes of arthritis. These include rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), which are typically negative and may assist in excluding alternative diagnoses such as rheumatoid arthritis, as well as serum uric acid levels when gout is considered in the differential diagnosis. When a systemic involvement is suspected, more investigations could be done by other clinical assessments and tests. To sum up, laboratory diagnostics regarding reactive arthritis mostly serve a supportive and exclusionary role, instead of providing a definitive confirmation. The interpretation of laboratory results should always be combined with the above-mentioned clinical findings and a detailed patient history to make an accurate diagnosis.

7.4. Synovial Fluid Analysis

Synovial fluid analysis is an important component during the diagnostic process of patients with suspected acute arthritis, first and foremost to exclude septic arthritis and crystal-induced arthropathies. In reactive arthritis, synovial fluid findings are normally consistent with an inflammatory but non-infectious process.

In the synovial fluid of patients with reactive arthritis there can often be seen an elevated leukocyte count, normally ranging from approximately 10,000 to 50,000 cells/ μ L, with a dominance of

neutrophils.(7) These data show active inflammation but are non-specific to reactive arthritis and could also be observed in other inflammatory joint diseases.(1)

An essential diagnostic feature when taking synovial fluid in the diagnostic workup is the absence of detectable pathogens within the synovial fluid. Gram staining and bacterial cultures should be negative, in contrast to septic arthritis, strengthening the classification of reactive arthritis as a “sterile” arthritis, even if it has a clear association with a preceding infection. This differentiation is important because septic arthritis needs immediate antimicrobial treatment and joint drainage to prevent a worse disease outcome, whereas reactive arthritis is managed differently.(1)

Even though molecular techniques such as polymerase chain reaction (PCR) could detect bacterial DNA, lipopolysaccharides or antigenic proteins in synovial fluid or tissue in some cases, these methods are not routinely used in clinical practice and are primarily applied in research settings.(7)

Therefore, the role of synovial fluid analysis in reactive arthritis remains largely focused on the exclusion of alternative diagnoses rather than confirmation of the disease.(1)

All in all, synovial fluid analysis in reactive arthritis demonstrates inflammatory characteristics without evidence of active infection or crystal deposition. Its primary value lies in differentiating reactive arthritis from septic arthritis and other causes of acute monoarthritis, making it important for the diagnostic process, especially when considering septic arthritis as a differential diagnosis.

7.5. Imaging

Imaging studies play an assisting role in the diagnosis of reactive arthritis and are mostly used to evaluate the extent of musculoskeletal involvement, detect complications, and exclude alternative diagnoses. In the early stages of the disease, imaging findings are often nonspecific or even normal, and therefore imaging is not required for diagnosis in all patients.

Conventional radiography is commonly used as an initial imaging modality in clinical practice. In acute reactive arthritis, radiographs are often normal or may show only soft tissue swelling. In cases of chronic or long-standing disease, radiographic changes such as joint space narrowing, periosteal reaction, enthesophyte formation, and erosions may be observed. Sacroiliitis may also develop, particularly in patients with chronic or axial disease, although these changes typically appear in later stages and may not be detectable on early radiographs.(1)

Magnetic resonance imaging (MRI) has a higher sensitivity than radiography regarding the detection of early inflammatory changes, especially in the sacroiliac joints and spine. MRI can show bone marrow oedema, synovitis, and enthesitis even before structural damage becomes visible on conventional imaging. Therefore, MRI is especially useful in patients where axial involvement has a high possibility or when the diagnosis is uncertain.(1,7)

Ultrasound has been increasingly recognized as a valuable, non-invasive imaging tool in the assessment of peripheral manifestations of reactive arthritis. It allows for the detection of synovitis, enthesitis, and tenosynovitis and may identify abnormalities not evident on clinical examination.(1,30)

Although these advantages exist, imaging findings in reactive arthritis are not specific and must be still interpreted within the clinical context. Imaging can be useful in observing patterns that resemble the clinical picture of spondyloarthritis, can help to monitor the disease progression and the exclusion of other conditions such as fractures, osteoarthritis, or septic arthritis. Therefore, imaging modalities give complementary information in the evaluation of reactive arthritis which can help in the larger context of the disease progression as well as differential diagnosis but are not required for diagnosis in typical cases. Mostly imaging is used to support the clinical assessment, detect early or chronic structural changes, and guide further management when necessary.

7.6. Differential Diagnosis

The differential diagnosis of reactive arthritis includes several inflammatory, infectious, and crystal-induced joint diseases that all can present with overlapping clinical features. Accurate differentiation during the diagnostic workup is essential, as management strategies and prognostic implications differ largely between these different conditions.

One of the most important conditions to exclude first hand is septic arthritis, which is a true medical emergency. It most commonly presents as an acute monoarthritis, and identification of microorganisms in synovial fluid remains the diagnostic standard. The difference to reactive arthritis is that the synovial fluid is sterile. Because delayed recognition of septic arthritis may result in higher morbidity and mortality, it must be considered in patients presenting with acute arthritis.(1,34)

Crystal-induced arthropathies, including gout and calcium pyrophosphate deposition disease, can sometimes also mimic reactive arthritis in everyday clinical practice, particularly if patients present with acute monoarthritis or oligoarthritis. In the above mentioned conditions, synovial fluid analysis is central for differentiation, as an identification of monosodium urate or calcium pyrophosphate crystals drives the diagnosis to crystal-associated arthritis instead of reactive arthritis.(35)

Rheumatoid arthritis should also be considered, especially in patients who report more persistent or polyarticular disease patterns. In the diagnostic evaluation, rheumatoid factor and anti-citrullinated protein antibodies may help support an alternative diagnosis, whereas reactive arthritis typically belongs to the seronegative spondyloarthritis spectrum.(1,27)

Other forms of spondyloarthritis, including ankylosing spondylitis, psoriatic arthritis, and inflammatory bowel disease-associated spondyloarthritis, overlap clinically with reactive arthritis because of some shared features, for example inflammatory back pain, enthesitis, dactylitis, and ocular manifestations. In these cases, differentiation relies on the broader clinical context, especially the presence or absence of a preceding infection, associated extra-articular features such as psoriasis or inflammatory bowel disease, and the overall disease course.(36)

Viral arthritis may also be addressed in the differential diagnosis, especially when patients present with acute-onset polyarticular symptoms and an appropriate epidemiological context, such as a travel history. This distinction is important because viral arthritis can look similar to inflammatory rheumatic disease in the early phase.(37,38)

Another important differential diagnosis is Lyme disease, as it can present with arthritis and should therefore be considered. A specific rash and the epidemiological background could hint towards Lyme, which can be treated by antibiotics.(39)

To sum up, the differential diagnosis of reactive arthritis calls for careful clinical evaluation supported by a precise anamnesis, laboratory testing and synovial fluid analysis. Exclusion of septic arthritis has a high priority, while recognition of features suggesting crystal arthropathy, rheumatoid arthritis, other spondyloarthritides, or viral arthritis helps guide appropriate diagnosis and management.

8. Treatment

8.1. General Principles of Treatment

The treatment of reactive arthritis aims to relieve articular and extraarticular symptoms, control the inflammation, management or treatment the triggering infection if appropriate, as well as reduce the risk of persistent disease and long-term functional impairment. Because reactive arthritis is different in many patients and the condition presents with varying severity and duration, treatment strategies should match every patient according to the clinical presentation, disease course, which phase the disease is showing and the presence of extra-articular manifestations.

During the acute phase, the first therapeutic goals are the reduction of pain and inflammation, preservation of physical function, with the aim of an improvement of life quality. In patients with persistent or recurrent disease, management must also address the risk of chronic synovitis, axial involvement, and long-term disability. Therefore, treatment often requires a short-term symptomatic control as well as a longer-term anti-inflammatory therapy in selected cases.(1)

An important principle in the management of reactive arthritis is the differentiation between treatment of the inflammatory arthritis itself and treatment of the triggering infection. In cases associated with urogenital infection, particularly *Chlamydia trachomatis*, antimicrobial therapy may be indicated to treat the underlying infection and reduce further transmission as well as control its symptoms. However, once arthritis has developed, eradication of the pathogen does not result in resolving of joint inflammation, as immune-mediated mechanisms may persist after the initial infection has receded.(1)

The decision for the correct therapy is also influenced by disease severity and pattern of involvement. Mild peripheral arthritis may respond to symptomatic therapy alone, but more severe or prolonged cases may require glucocorticoids, conventional disease-modifying antirheumatic drugs, or, in selected resistant cases, biological therapy. The presence of enthesitis, axial manifestations, or significant extra-articular disease may further influence treatment choices and follow-up, as well as consultation of other specialities.(1)

Supportive non-pharmacological measures, including rest during periods of marked inflammation, physiotherapy, maintenance of joint mobility, and gradual return to activity, may also contribute to recovery and help prevent functional decline.(1,40)

All in all, treatment of reactive arthritis needs to be adapted regarding the stage of disease and has to be managed individually with a combination of symptomatic relief, management of infection where appropriate, and escalation of anti-inflammatory therapy in persistent disease.

8.2. Non-Steroidal Anti-Inflammatory Drugs and Symptomatic Therapy

Non-steroidal anti-inflammatory drugs (NSAIDs) are considered the first-line pharmacological treatment for reactive arthritis and are mainly used for pain and inflammation control during the acute phase of the disease. In many patients with peripheral joint involvement, NSAIDs provide a good symptomatic relief and can often be sufficient as initial therapy, mainly in mild or self-limiting cases, however, they do not prevent chronicity.(1,41)

In clinical practice, the selection of NSAID therapy is based on general patient-related factors and tolerability. Commonly used agents include standard NSAIDs like ibuprofen, naproxen and diclofenac. Their clinical efficacy has been supported mainly by physicians' experience, while formal evidence is limited to only a small number of prospective studies. There is no clear evidence that one specific NSAID is superior to another in reactive arthritis; therefore, appropriate dosing and treatment duration are important for effective symptom control.(1)

However, in patients with more severe or persistent disease, NSAIDs alone are often insufficient to control inflammation over the long term.(41)

Symptomatic treatment also includes non-pharmacological supportive measures. During periods of marked inflammation, temporary reduction of physical load may help relieve pain; however, prolonged immobilization should be avoided, as it may contribute to stiffness and functional decline. Physiotherapy and guided exercise are therefore important components of management, helping to maintain joint mobility, muscle strength, and overall physical function.(40) Cryotherapy should also be considered.(41)

The choice of using analgesia may also be considered in selected patients, especially when pain doesn't pause after anti-inflammatory treatment. However, symptomatic pain relief should not replace appropriate anti-inflammatory management and clinical reassessment in patients with persistent disease activity.

To sum up, NSAIDs as well as supportive symptomatic measures form the foundation of initial treatment in reactive arthritis and can lead to a favourable outcome. They are especially useful in acute and mild disease, but as they show shortcomings in prolonged or more aggressive cases a additional escalation of therapy in selected patients is needed.

8.3. Glucocorticoids

Glucocorticoids are used in reactive arthritis when non-steroidal anti-inflammatory drugs do not provide sufficient enough symptom control or are not tolerated. Their role is mainly as a short-term anti-inflammatory option and not useful as a long-term maintenance therapy.(1,41)

Intra-articular glucocorticoid injections should be considered in patients with acute reactive arthritis, particularly after inadequate response to NSAIDs, which is reached when for two weeks at

least two different NSAIDs at full dose do not provide symptomatic relief.(1) When they work, intra-articular glucocorticoids may provide symptomatic relief while avoiding some of the adverse effects associated with systemic glucocorticoid therapy. According to recent review data, intra-articular corticosteroid therapy is generally regarded as a second-line option, especially in moderate to severe arthritis or after failure of first-line treatment.(1,39)

Systemic glucocorticoids may be used in selected cases, but their role is more limited and should generally remain short-term. Overall, glucocorticoids represent an effective option for control of persistent inflammation in selected patients, especially when local treatment is possible, but they do not replace the need for further therapeutic escalation in prolonged or refractory disease.(1,39)

8.4. Disease-Modifying Antirheumatic Drugs

Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) are mainly used in patients with persistent or chronic reactive arthritis, rather than in those with acute, self-limiting disease. In clinical practice, they are generally considered when first-line and symptomatic treatment, as well as second-line treatment, does not provide sufficient control of inflammation and symptoms.(1,42)

Among csDMARDs, sulfasalazine has been studied most extensively in reactive arthritis. Reviews consistently describe it as the conventional agent with the strongest direct evidence in chronic or more severe disease, although the overall evidence remains limited. In a randomised double-blind placebo-controlled trial, sulfasalazine was associated with only a modest short-term benefit, and no significant difference between treatment groups was observed after 6 months in the intention-to-treat analysis. In addition, treatment discontinuation because of adverse effects, mainly gastrointestinal, was more frequent in the sulfasalazine group.(1,26,42)

Methotrexate is also used in clinical practice, particularly in chronic reactive arthritis, but the supporting evidence is considerably weaker. Current reviews note that methotrexate is commonly prescribed, yet its efficacy has not been confirmed in clinical trials specifically addressing reactive arthritis. Its use therefore appears to rely more on clinical experience than on robust trial-based evidence.(1,26)

Overall, csDMARD therapy may be considered in patients with persistent peripheral inflammatory disease when symptomatic measures alone are insufficient. Of the conventional agents, sulfasalazine has the most direct supporting evidence, although that evidence is limited and not uniformly positive. Methotrexate remains an empirically used option, but stronger evidence for its effectiveness in reactive arthritis is still lacking.(1,26,42)

8.5. Antibiotic Therapy

Antibiotic therapy in reactive arthritis has two distinct contexts: treatment of the triggering infection and, more controversially, attempted modification of the subsequent arthritic disease course. In cases of urogenital reactive arthritis associated with *Chlamydia trachomatis*, antimicrobial therapy is indicated to treat the underlying infection. However, once arthritis has become clinically established, the effect of antibiotic treatment on joint manifestations is less certain.(1,43)

Several reviews emphasize that eradication of the initial infection does not necessarily result in resolution of arthritis, as the inflammatory process may persist after the acute infectious episode. More generally, antibiotic treatment of established reactive arthritis has not shown consistent benefit across studies.(1,43)

The question of prolonged or combination antibiotic therapy remains particularly controversial in chronic *Chlamydia*-associated reactive arthritis. In a double-blind, placebo-controlled trial, a 6-month course of combination antibiotics in patients with PCR-positive chronic *Chlamydia*-induced reactive arthritis was associated with significantly better clinical responses than placebo.

Nevertheless, this evidence applies to a selected subgroup, and the broader literature does not support routine prolonged antibiotic treatment for unselected patients with reactive arthritis.(1,44)

Overall, antibiotic therapy is clearly relevant for the treatment of an active triggering infection, especially in urogenital disease, but its role in changing the following course of reactive arthritis remains limited and context dependent. At present, management of established arthritis relies primarily on anti-inflammatory and immunomodulatory strategies, while prolonged antibiotic therapy may be considered only in selected chronic *Chlamydia*-associated cases supported by microbiological evidence.(1,43,44)

8.6. Biological Therapy

Biological therapy may be considered in a small subset of patients with persistent, severe or refractory reactive arthritis after failure of conventional treatment. However, the evidence base remains limited and consists predominantly of case reports, case series, and small observational data rather than large controlled trials.(25,45)

Among biologic agents, tumor necrosis factor inhibitors are the best studied in reactive arthritis. Their use is biologically plausible because TNF- α has been implicated in chronic inflammatory pathways in reactive arthritis, and published reports suggest that anti-TNF agents such as infliximab, adalimumab, and etanercept may lead to clinical improvement in selected refractory cases. Nevertheless, the available evidence remains insufficient to support broad routine use.(25,45) More recently, other targeted agents have also been discussed. The 2020 review by Zeng et al. noted that evidence for IL-17-targeted therapy in reactive arthritis was limited to very few reports,

including a single case treated with secukinumab, and concluded that more studies were needed. A newer 2024 review similarly identified anti-IL-17 and anti-IL-6 therapies as potential options in refractory disease, but again emphasized that the available data are derived mainly from case reports and case series.(25,45)

Available reviews suggest that biologic therapy has generally been well tolerated in reported cases, with a low incidence of major adverse events. Even so, treatment decisions should remain individualised because current evidence is still limited and controlled trial data are lacking.(25,45) Overall, biologic therapy should be regarded as a reserved option for refractory reactive arthritis when conventional treatment has failed. At present, TNF inhibitors have the strongest supporting evidence among biologic agents, whereas IL-17- and IL-6-directed approaches remain promising but insufficiently studied.(25,45)

8.7. Prognosis and Treatment Outcomes

The prognosis of reactive arthritis is not the same in different patients and depends on the severity of the initial disease, the persistence of triggering factors, and individual host characteristics. In many patients, reactive arthritis shows a self-limiting course, with resolution of symptoms within several months. However, a significant number of patients develop recurrent or even chronic disease, which may require a prolonged anti-inflammatory or immunomodulatory treatment.(1,26) In patients with mild acute disease, treatment with NSAIDs and supportive measures is often sufficient to achieve satisfactory symptom control and recovery.(1) Local glucocorticoid therapy may further improve outcomes in those with limited joint involvement.(1) These patients generally have a favourable prognosis, especially when inflammation resolves within the first few months and no major extra-articular or axial manifestations are present.

By contrast, patients with persistent peripheral arthritis, axial involvement, pronounced enthesitis, or recurrent episodes are more likely to experience long-term disease burden.(1,23,24) In such cases, escalation to csDMARDs or, in selected refractory patients, biologic therapy may be necessary to control inflammation and preserve function.(1,25,41) The effect of these therapies is variable, indicating the heterogeneity of the disease and the limited evidence base for advanced and newer treatment strategies in reactive arthritis.(25,41)

Numerous factors have been associated with worse outcomes. HLA-B27 positivity is one of the most consistently reported predictors of prolonged disease duration, recurrence, and axial involvement.(23,24) Persistent infection, particularly with *Chlamydia trachomatis*, may additionally contribute to ongoing immune stimulation and chronic inflammation.(12,15) Additional clinical and host-related factors may also influence the course of disease.

Treatment outcomes are therefore closely linked to the underlying pathophysiology of reactive arthritis. In some patients, elimination of the initial infection and symptomatic control of inflammation are sufficient for recovery.(1) In others, persistent bacterial components and dysregulated immune responses appear to sustain chronic disease despite treatment.(12,15) This explains why therapeutic success is often greatest in acute, limited disease and more difficult to achieve in chronic or refractory cases.

Overall, most patients with reactive arthritis have a relatively good prognosis, but a clinically important minority can develop chronic, relapsing, or more severe disease patterns, which then leads to the need for a long-term management.(1,26) Early recognition, appropriate treatment, and identification of risk factors for chronicity are therefore key for improving outcomes and decreasing long-term functional impairment.

9. Discussion

9.1. Main findings of the review

This literature review shows that arthritis associated with urogenital infections is most likely represented by reactive arthritis, especially in relation to *Chlamydia trachomatis*.(1,11) Regarding the most common genitourinary triggers, *C. trachomatis* is most frequently reported, whereas a broader spectrum of additional infectious agents is described less often and mostly in a non-classical or case-based context.(1,2,11) Reactive arthritis is therefore best understood as a post-infectious inflammatory condition which is characterised by sterile synovitis after an extra-articular infection, which has heterogeneous definitions and a lack of universally established diagnostic or classification criteria.(1,11)

When looking at pathogenesis, a multifactorial interaction between microbial factors, immune dysregulation, and host susceptibility is supported by the reviewed literature.(1,11) There is evidence that suggests the persistence of microbial components, especially in chlamydia associated reactive arthritis, which gives a logical explanation for ongoing synovial inflammation after resolution of the initial mucosal infection, even after treatment of this.(12,15) This can lead to chronicity and disease manifestation, which is explained through immunological data that suggests that responses are shifted towards an imbalance in Th1 and Th17, in favour of more Th17 where Th1 would be more important to eliminate the bacterial remnants. Th17 is not as competent in eliminating these and further triggers a pro-inflammatory cytokine cascade, where it most importantly activates IL-17 and TNF- α , which leads to manifestations known from the spondylarthritis spectrum.(11,20,21)

HLA-B27 seems to modify susceptibility and disease course but is not alone an explanation for disease development in general, or its strength of manifestation.(23,24) Clinically, reactive arthritis has a broad spectrum, typically presenting with asymmetric oligoarthritic of the lower extremities with frequent enthesitis and characteristic extra-articular manifestations.(1,11) It is primarily a clinical diagnosis, stressed by many diagnostic publications, which is supported by evidence of a preceding infection and exclusion of differential diagnosis, rather than a single definitive test.(1,11) Treatment is commonly approached in a stepwise manner, starting by NSAIDs as a first line therapy, with glucocorticoids and csDMARDS as a second line therapy in persistent peripheral disease. Antibiotic therapy is mainly indicated for treating the triggering infection, with a limited and variable impact on established arthritis and an uncertain, not evidently indicating effect, as there are contradicting trials.(1,11) If a patient has refractory symptoms or episodes, therapy with biologicals could be beneficial, but to this date the evidence base is mainly from case series, small studies and case reports, which shows the need for more advanced research.(25,45) All in all, the reviewed literature supports with evidence that reactive arthritis is a clinically relevant but

pathogenetically complex condition. There are many uncertainties, especially regarding diagnostic and therapeutic standardisation strategies, which justify the discussion of limitations and future research directions in the following sections.

9.2. Strengths and limitations of the current literature

The relationship between immune dysregulation, inflammatory joint disease and preceding infection which is a useful foundation in understanding reactive arthritis is well explained in current literature.(1,11) Bringing together the multidimensional aspects of reactive arthritis is the biggest upside of the literature regarding this syndrome, as it describes in detail and in a larger perspective the microbiological, clinical, therapeutic and immunological aspects.(1,11,26) Especially, literature supporting *Chlamydia trachomatis* as the most established urogenital trigger with a plausible pathogenetic frame involving persistence-related mechanisms, cytokine-mediated inflammation, and host susceptibility is commonly found across many decades of research.(1,11,15,16)

Recurrence of these themes across reviews, mechanistic studies and clinical reports shows that there is strong evidence overall for the concept model of reactive arthritis.(1,11)

Another strength of the available evidence is the combination of different publications, such as foundational mechanistic studies and more recent review literature.(1,15) There are earlier molecular and immunological studies that are still highly relevant because they could establish key concepts such as synovial persistence of chlamydial material, host inflammatory signalling as well as the modifying role of HLA-B27.(9,24) Newer reviews helped to integrate these earlier findings into a broader clinical and therapeutic framework.(1,11) Considering this, the combination of older mechanistic work and newer synthesising reviews allows a comprehensive interpretation of the disease, rather than each of these different earlier findings alone could provide.(1) Nevertheless, the current evidence base has important limitations.(1,11) Even if newer studies continue to appear, many seem to remain based on a relatively small patient population, retrospective designs, case series or more narrowly focused research questions.(1,25,45) This is a limiting factor regarding reactive arthritis, as the study populations are heterogeneous, diagnostic definitions are not completely standardized and the interval between infection and arthritis complicates patient selection and comparison across these studies.(1,26)

Furthermore, the literature is often fragmented and many studies focus on a single aspect of reactive arthritis, such as bacterial persistence, immunological pathways, or treatment response, without integrating these findings into the broad clinical framework that reactive arthritis represents.(1,11,15,25) Therefore, few studies connect all the aspects, such as pathophysiology, clinical phenotypes, diagnostic uncertainties and varying therapeutic outcomes within the same analysis.(1,11,25) A comprehensive study which allows a conclusion about how individual

pathogenetic mechanisms relate to disease heterogeneity, chronicity and treatment response would be interesting, as this seems limited today.(1,11) It is also still methodologically challenging that there is an absence of a universally accepted diagnostic or classification criterion for reactive arthritis.(1) As reactive arthritis is still primarily a clinical diagnosis, study populations may differ heavily depending on how authors define and classify the disease.(1,26) This causes a reduced comparability between studies and could explain the variation in the reported clinical patterns, pathogen detection rates and treatment outcomes.(1,11,26) Additionally, most pathogenetic studies are older, which shows that several key mechanisms of the disease were established early on and newer literature mostly provides broader synthesis and less often large, integrative original studies.(1,9) However, the literature on reactive arthritis is scientifically valuable and enough to support a logical multifactorial model of the disease(1,11) It is still limited due to the methodological heterogeneity, small cohort, fragmented evidence and in some cases insufficient integration of microbiological, immunological and therapeutic domains.(1,25,45) When interpreting newer therapeutic findings this becomes especially important, as it is difficult to convert these into more precise diagnostic or treatment strategies.(25,26,45)

9.3. Biological therapy and unresolved mechanistic questions

There is a new development in the up-to-date literature regarding reactive arthritis and the discussion on biological therapy in chronic or refractory disease.(25,45) The evidence is still limited, however, especially treatment with TNF-Inhibitors show a better clinical outcome in specific refractory disease courses.(25,45) These clinical observations match with in this thesis discussed mechanisms of cytokine-mediated inflammatory pathways and networks, which form and build up, leading to persistent disease courses.(25) Regarding IL-17-mediated mechanisms and reactive arthritis, the evidence is much thinner but is seen as relevant in the broader literature as reactive arthritis is seen as part of the spondyloarthritis spectrum, where this mechanism is discussed as a relevant feature in the pathogenesis.(20,45) At the same time, the success of biological therapy in some cases should not be seen as evidence that the pathogenesis is fully understood in all aspects. That biologicals can be therapeutically useful shows the importance of specific inflammatory pathways, for example TNF-associated pathways, however it does not fully explain how the different pathways are triggered, maintained, interact with each other or show different severity in different patients.(25) Especially the question about the difference between patients with a self-limiting disease course and patients who develop a recurrent, persisting or even chronic disease course is therefore not fully grasped.(25) First and foremost, in reactive arthritis this differentiation is specifically relevant, as the disease is clinically located between infectious triggering and immune-mediated synovitis.(25) Persistence, especially regarding *Chlamydia*

trachomatis triggered reactive arthritis, and infectious stimuli work in combination with immunological amplification as shown in the literature, which denies the thought that biologicals work in an isolated immunological manner.(9,12,25) Biologicals can interact downstream on inflammation signalling and limit these and the symptoms, without explaining where biologicals in the cascade of the initial triggering infection, the following persistence and amplification of antigens, with a subsequent immune polarisation and resulting clinical picture, its mechanism is working. It is yet to be completely understood and standardised and therefore fully explainable.(25) Therefore, a difference between the therapeutic possibility of targeting specific interactions in the pathogenesis and its complete understanding is made in the literature.(25) There is literature that can show the connection between concepts of cytokine-mediated inflammation and persistence, whereas the specific and definite mechanism with individual disease courses and phenotypes is only partly characterised.(9,12,25) Another limitation is that the evidence regarding biological therapy in reactive arthritis is mostly from small studies, case series and case reports, with nearly no large randomised controlled studies which could provide good indications for clinical guidelines.(25,45) However, the case studies give hope regarding its effects on clinical symptoms and disease course but leave questions open regarding the selection of patients, the right timing, the long-term disease course as well as the relationship between a good response to therapy and the underlying mechanism.(25,45) All in all, biological therapy is an important aspect regarding the current discussion about reactive arthritis, as it shows progression regarding therapy options and outcomes but at the same time points out remaining uncertainties.(25,45) The discussion demonstrates that targeted immunological intervention can be successful in specific chronic and refractory cases, without giving a complete explanation about the underlying pathogenesis. Therefore, the literature does not only give potential solutions but also marks possible theories that should be addressed in future prospective studies that are methodologically more advanced.(25,45)

9.4. Safety and clinical implications

Safety is a key part of treatment decisions in reactive arthritis, especially when care needs to go above just treating symptoms.(1,41) Because reactive arthritis follows an infection, treatments that affect the immune system need careful evaluation, especially for patients whose disease lasts or does not respond to standard care.(1) For first-line treatments like NSAIDs and glucocorticoids, safety matters are similar to those in other rheumatic diseases. Known side effects should be evaluated against the expected benefits. It is recommended that NSAIDs is used as the first treatment and it is advised to use them carefully, with regular reassessment if patients do not improve. This shows the need to balance risks and benefits.(1,39)

When glucocorticoids are needed, giving them directly into the joint is preferred. This targets inflammation locally and reduces side effects, showing a focus on safety.(1,39) Safety becomes more complicated when csDMARDs or biologic drugs are used for long-lasting or hard-to-treat cases.(41) Zeng et al. note that biologic drugs, especially TNF inhibitors, have been used in tough cases of reactive arthritis. However, more evidence needs to be conducted, so it is hard to fully judge long-term safety.(25) Mullokulov et al. also point out that while biologics can help some patients, the lack of strong clinical trial data makes it hard to draw conclusions about how well they work and how safe they are.(41) Because of this, side effects and infection risks from biologic therapy in reactive arthritis are not as well studied.(25,41)

This gap between reports of improvement and detailed safety analysis is a weakness in current research on these treatments, even if no severe infection or spreading of viruses has been seen.(25) Clinically, these points reveal why it is important to adapt treatment to each patient, considering how severe and long-lasting the disease is and how the patient has responded to past treatments. For patients with short-term or mild disease, treating symptoms with NSAIDs may be enough, so stronger immune-modifying drugs can be avoided. On the other hand, for chronic or hard-to-treat diseases, stronger treatments may be needed.(1)

Overall, research suggests that advanced immune therapies can help some patients with ongoing reactive arthritis. Still, their use should be considered carefully because the disease is linked to infection and safety data are limited.(1,25,41)

More well-designed studies are needed to better understand the long-term safety of csDMARDs and biologic drugs in reactive arthritis.(20,33)

9.5. Future directions

Research on reactive arthritis is limited by differences in study methods, small sample sizes, and inconsistent diagnostic definitions. These issues make it hard to compare studies and weaken the conclusions that can be drawn.(1,41) To deal with these issues, upcoming research should include larger prospective studies with well-defined and similar patient groups. Another key challenge is that there are no universally accepted criteria for diagnosing or classifying reactive arthritis.(1) Since reactive arthritis is mainly diagnosed based on clinical signs, differences in how cases are defined can largely affect reported symptoms, detection of pathogens, and treatment results.(1) Future studies could benefit from using standardised diagnostic systems that consistently include prior infections, joint symptoms, other related findings, and supporting lab data. Especially for women, this could be important, as they can experience asymptomatic urogenital infection and differences in sampling strategies can complicate pathogen detection, which stresses the potential value of an accessible nucleic acid amplification-based diagnostic approach.(31–33) The literature

also shows that microbiological, immunological, and clinical findings are not yet fully combined into a single disease model.(1,41) Ongoing microbial presence, immune responses, and genetic factors all play a role in disease development, but how they interact to shape symptoms and disease course is still not fully understood.(1,41) A more integrated research approach is likely to help explain why some patients recover quickly while others develop long-lasting or recurring arthritis. One more key area for future research is how disease mechanisms relate to how patients respond to treatment.(25,41) Biologic therapies may help some patients who do not respond to other treatments, but most evidence comes from case reports, small series, and a few observational studies.(25) Because of this, it is still unclear which patients will benefit most from targeted therapies, which inflammatory pathways matter most, and how treatment response connects to the disease's biology.(25,41) Future studies could make a big impact by combining treatment evaluation with more precise ways of grouping patients based on clinical and biological features. Long-term safety and outcomes are still not well understood, especially for immunomodulatory and biologic treatments.(1,25) Many studies report little on safety and have short follow-up periods, making it hard to judge long-term tolerability and risks of infection.(25) Better safety reporting and longer follow-up would make future treatment research much more useful for clinical practice. Overall, moving research on reactive arthritis forward will likely have a need of better standardization of methods, closer integration of microbiological and immune data, and stronger prospective treatment studies.(1,25,41) These improvements could lead to more accurate diagnoses, more specific treatments, and a better understanding of the differences between patients.

10. Conclusion

Reactive arthritis after urogenital infection is a complex inflammatory condition. It develops when persistent microbes, an overactive immune system and genetic factors work together with autoimmunity to cause joint inflammation and extra-articular manifestations. Of potential triggering urogenital pathogens, *Chlamydia trachomatis* is the most common trigger. Research has shown that ongoing bacterial presence and subsequent inflammation by cytokine pathways are the key factors in developing the disease and the risk for chronicity. Reactive arthritis can look different from person to person but in most cases, it presents as an asymmetric oligoarthritis mainly affecting the lower extremities and is often accompanied by enthesitis, dactylitis and extra-articular symptoms, such as urogenital, ocular and mucocutaneous manifestations, which are important diagnostic clues and show the systemic nature of the disease. Regarding the diagnosis of reactive arthritis, it still is primarily clinical and is based on the temporal relationship between a preceding infection, the characteristic musculoskeletal and extra-articular manifestations, supportive laboratory findings as well as the exclusion of differential diagnosis. There is no single laboratory or imaging test that is definite, which is an important challenge, as consequently no universally accepted diagnostic criteria is defined for clinical practice and research. When treating of reactive arthritis, a stepwise and individualised approach is needed. Non-steroidal anti-inflammatory drugs remain the foundation of the initial therapy, while glucocorticoids come next, with an escalation to conventional disease-modifying antirheumatic and after those, biologicals in chronic or refractory cases. The escalation of therapy offers a benefit regarding symptoms and outcomes, but current evidence is still limited regarding safety and precise outcome projections. Antibiotic therapy is needed, especially in the beginning, for treating the triggering infection, first and foremost in urogenital disease. However, the effect of prolonged antibiotic treatment on established arthritis remains uncertain and is not recommended. All in all, reactive arthritis is a clinically relevant and pathogenetically complex disease, following infection. Advances regarding this disease are clear, but there are still uncertainties regarding the pathogenesis, diagnostic standardisation, disease heterogeneity and long-term treatment strategies.

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