



Reactive Arthritis Update: Spotlight on New and Rare Infectious Agents Implicated as Pathogens

Henning Zeidler¹ · Alan P. Hudson²

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Abstract

Purpose of Review This article presents a comprehensive narrative review of reactive arthritis (ReA) with focus on articles published between 2018 and 2020. We discuss the entire spectrum of microbial agents known to be the main causative agents of ReA, those reported to be rare infective agents, and those reported to be new candidates causing the disease. The discussion is set within the context of changing disease terminology, definition, and classification over time. Further, we include reports that present at least a hint of effective antimicrobial therapy for ReA as documented in case reports or in double-blind controlled studies. Additional information is included on microbial products detected in the joint, as well as on the positivity of HLA-B27.

Recent Findings Recent reports of ReA cover several rare causative microorganism such as *Neisseria meningitides*, *Clostridium difficile*, *Escherichia coli*, *Hafnia alvei*, *Blastocystis*, *Giardia lamblia*, *Cryptosporidium*, *Cyclospora cayetanensis*, *Entamoeba histolytica/dispar*, *Strongyloides stercoralis*, β -haemolytic *Streptococci*, *Mycobacterium tuberculosis*, *Mycoplasma pneumoniae*, *Mycobacterium bovis* bacillus Calmette-Guerin, and *Rickettsia rickettsii*. The most prominent new infectious agents implicated as causative in ReA are *Staphylococcus lugdunensis*, placenta- and umbilical cord-derived Wharton's jelly, *Rothia mucilaginosa*, and most importantly the SARS-CoV-2 virus.

Summary In view of the increasingly large spectrum of causative agents, diagnostic consideration for the disease must include the entire panel of post-infectious arthritides termed ReA. Diagnostic procedures cannot be restricted to the well-known HLA-B27-associated group of ReA, but must also cover the large number of rare forms of arthritis following infections and vaccinations, as well as those elicited by the newly identified members of the ReA group summarized herein. Inclusion of these newly identified etiologic agents must necessitate increased research into the pathogenic mechanisms variously involved, which will engender important insights for treatment and management of ReA.

Keywords Reactive arthritis · HLA-B27 · COVID-19 virus · Vaccination · Antimicrobial therapy

Introduction

The association between microbes and joints has attracted medical interest for decades and more, and that association remains a complex issue. The World Health Organization, in association with the Arthritis and Rheumatism Research

Council, classified the relationship between joints and infection into the following four groups [1]:

Group I: This group includes septic or infectious arthritis with the causative organism identified in joints secondary to an infection elsewhere in the body.

Group II: This group comprises post-infectious arthritis with bacterial antigens being detected in the joint.

Group III: This group includes reactive arthritis (ReA), with the infection originating in the urogenital or gastrointestinal system causing inflammatory joint disease; however, the microbes are usually not detected in the joint.

Group IV: This group consists of inflammatory arthritis triggered by microbes, where neither the organism nor

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✉ Henning Zeidler
zeidler.henning@mh-hannover.de

¹ Division of Clinical Immunology and Rheumatology, Hannover Medical School, Carl-Neuberg-Straße 1, 30625 Hannover, Germany

² Department of Biochemistry, Microbiology, and Immunology, Wayne State University School of Medicine, Detroit, MI, USA

its product or specific antigen is established in the joint.

The term ReA was introduced by Ahvonen and colleagues [2] to describe acute arthritis triggered by an extra-articular bacterial infection, often in the gastrointestinal or urogenital tract, and in which the causative organism cannot be cultured from synovial specimens. After discovery of the association between HLA-B27 and ReA [3], the term “HLA-B27 associated reactive arthritides” became common, preferentially following infections with *Enterobacteria* and *Chlamydia*. The disease was classified as a subgroup within the family of spondyloarthritis, also termed reactive spondyloarthritis [4]. However, several other arthritides fulfil the original definition, which has led to the suggestion that ReA can be divided into a B27-associated and non-associated form [5]. The statement that arthritides developing after a distant infection are called reactive or post-infectious [6] is contrary to the proposal that they also should be called ReA [5].

Over time it has become evident that patients with typical ReA have microbial antigenic material, bacterial DNA and RNA and even metabolically active, persistent microbes in the synovial fluid or synovial tissue of affected joints [c.f. [7–9]]. Thus, the differentiation between post-infectious arthritis and ReA has been blurred and the diagnosis is made largely on the basis of clinical findings, medical history, and the direct and/or indirect detection of a pathogen. An option to overcome the pathogenic overlap between reactive and post-infectious in terminology might be to postulate two types of ReA: (a) “infection reactive” arthritis, characterized by the intra-articular persistence of viable, metabolic active though non-cultivable bacteria, such as shown for *Chlamydia*, and (b) “infection triggered reactive arthritis” [7]. In the latter, bacterial antigens derived from viable bacteria elsewhere in the body are disseminated to the joints, causing an immune-mediated arthritis. Generally, differentiation between post-infectious arthritis and ReA seems no longer terribly relevant. We therefore suggest that the use of the term “ReA” is preferable overall, as the clinical features are now established, even though no universal agreement on classification and diagnostic criteria currently exists [8].

With these indicated basic considerations related to changing disease terminology, definition, and classification over time in mind, we present a comprehensive review, with a focus on articles published between 2018 and 2020. An update is given for the microorganisms established as the main causatives of ReA, those identified as rare infective agents, and those indicated as new candidates causing ReA. Even given the diverse terminological and classification discussion summarized, we include in this review the full spectrum of infectious agents published under the term ReA.

Well-Established Primary Causative Agents of Reactive Arthritis

Reactive arthritis usually follows gastrointestinal infections by organisms from the genera *Yersinia*, *Salmonella*, *Campylobacter*, and *Shigella*, which most commonly follow dysenteric outbreaks. Alternatively, ReA often follows urogenital infection with *Chlamydia trachomatis* (Table 1). Asymptomatic triggering infections are reported in as many as 36% of ReA cases elicited by chlamydial, and 26% of cases elicited by enteric infection [c.f. 10]. The respiratory microorganism *Chlamydophila (Chlamydia) pneumoniae*, a common cause of bacterial infections worldwide, is now also well accepted as causative agent of ReA; however, ReA caused by this pathogen is less frequent than that caused by *C. trachomatis* [13]. Most patients infected with *C. pneumoniae* are asymptomatic, and the course of respiratory illness is usually relatively mild [14]. The identification of bacteria or bacterial products in the joint differs among the individual triggering agents, although thorough investigation has not always been done in every instance (Table 1).

Decreasing incidence of ReA has been reported in developed countries [15]. In contrast, a recent two-centre French retrospective study reported that the frequency of ReA in patients hospitalized in Rheumatology departments did not change between 2002 and 2012 compared with the period 1986–1996 [16••]. For both cohorts, diagnosis in the majority of cases was based on clinical characteristics alone, as microorganism could not be identified by culture or PCR in synovial fluid, or by serology. Microbes were only detected in about half the patients, with a significant decrease in the number of *Chlamydia trachomatis* infections between the two cohorts. The trigger for infection was predominantly urogenital and gastrointestinal infection, with similar distribution of the two in both cohorts. However, some “atypical” triggers, such as *Escherichia coli*, *Mycoplasma*, *Streptococcus pyogenes*, *Mycobacterium bovis* after bacillus Calmette-Guérin treatment, and *Strongyloides stercoralis*, were found in the 2002–2012 cohort but not in the 1986–1996 cohort. Monocentric evaluation of 67 patients diagnosed with ReA at the Centre Hospitalier Régionale et Universitaire, Besançon, France, also reports *Ureaplasma urealyticum* ($n=5$) and *Neisseriae gonorrhoeae* ($n=4$) as causative agents [17].

Hayes and colleagues performed a study to characterize perspectives of 548 members of the Canadian Rheumatology Association on evolving trends of the disease [18••]. Common investigations in ReA included inflammatory markers, HLA-B27, *Chlamydia* and gonorrhoea testing, stool cultures, synovial fluid analyses, and SI joint imaging. Nearly half of respondents believed that the incidence of ReA is declining and that causes of ReA may be changing. Rheumatologists reported that most of the ReA cases in their practices were caused by an unknown

Table 1 Bacterial species/groups known to be primary causes of HLA-B27 positive ReA, and identification of bacteria and bacterial products in the joint by various methods [modified from 10–12]

Entry site	Bacteria	Bacterial products
Urogenital tract	<i>Chlamydia trachomatis</i>	Antigens, DNA, RNA, short-lived primary ribosomal RNA transcripts (viability), aberrant organism by electron microscopy
Gastrointestinal tract	<i>Yersinia enterocolitica</i> O3, O8, and O9 <i>Y. pseudotuberculosis</i> <i>Salmonella enterica</i> serovars <i>Typhimurium enteritidis</i> , <i>Paratyphi B and C</i> , and others <i>Shigella flexneri</i> , <i>S. sonnei</i> and <i>S. dysenteriae</i> <i>Campylobacter jejuni</i>	Antigens, RNA, DNA Antigens, RNA Antigens, DNA Antigens, DNA DNA
Respiratory tract	<i>Chlamydia pneumoniae</i>	Antigens, DNA, RNA

organism, were sexually transmitted, or followed gastrointestinal infection. Thus, there may be a need to include investigations for rare and new infective agents eliciting ReA (see below). Recent studies regarding the frequency of *Chlamydia*-induced ReA were reviewed, with a focus on the question of whether the entity is in fact disappearing, or whether it is simply being underdiagnosed or underreported [19••]. Epidemiological reports indicate diversity in the frequency of *Chlamydia*-associated ReA in various parts of the world, with evidence of declining incidence in some regions. Moreover, no epidemiologic information is available for *Chlamydia pneumoniae*-associated ReA, a causative entity of chlamydial infection described in case studies simply as “less frequent” [c.f. 19••].

A review of ReA following *Chlamydia* infection in competitive sports reported two clinical cases and provides recommendations for their clinical management [20]. Both patients, football players, presented due to an atraumatic and pain-free swelling of the knee joint. Targeted sexual history and urogenital investigation for *C. trachomatis* by PCR in urethral swabs was essential for the diagnosis. Urinary PCR can also be used for the rapid diagnosis of ReA associated with *C. trachomatis*, as recently shown in a study investigating an Indian population [21•]. *C. trachomatis* DNA was detected from urinary samples by PCR in 24 (36%) of 65 ReA patients. PCR was negative in the patients with other inflammatory, arthritis as well as in a normal healthy control group.

Rare Infectious Agents Implicated in the Causation of Reactive Arthritis

Many other infectious agents have been reported to cause non-HLA-B27-associated arthritis labelled as ReA. The number has increased over the years, with considerable diversity in designation and classification, e.g. “new” candidates of arthritogenic agents [11], probable or potential agents [10], atypical causes of

ReA and variants of ReA [22], arthritis not associated with HLA-B27 [1], and possible causative agents [23]. The most recent update on ReA classified the arthritogenic agents associated with the development of the disease according to enteric infections (including amoebae—*Cryptosporidium*, *Giardia lamblia*—and the helminth *Strongyloides* spp.), urogenital infections, respiratory infections, and miscellaneous infections (including *Human immunodeficiency virus* (HIV) *Parvovirus B19*, *Borrelia burgdorferi*, *Calmette-Guerin Bacillus*, and *Chikungunya virus*) [24••]. Table 2 summarize the spectrum of infectious agents currently being referred to as initiating ReA, including information on the microbial products detected in the joint and regarding HLA-B27 positivity. The principal references documenting the additional information listed are summarized in a supplement to Table 2.

We deleted viral infections with *Chikungunya* virus and *Parvovirus* from the list of causative agents, since their clinical manifestations are heterogeneous and thus simulate different rheumatic conditions (for references see supplement to Table 2). The role of HIV infection in the causation of ReA remains unclear, i.e. whether it can cause the disease by itself or only in the context of concomitant infections typically causing ReA (for references see supplement to Table 2). Additional issues with possible HIV-related ReA include an apparent overlap of the features of reactive and psoriatic arthritis in some studies, as well as new ReA having been reported to emerge upon commencement of combination anti-retroviral therapy as a manifestation of immune reconstitution inflammatory syndrome [c.f. 26]. Other microorganisms, such as *Bacillus cereus*, *Helicobacter cinaedi*, *Lactobacillus*, and *Streptococcus salivarius*, listed in earlier reviews were not carried over here because case reports of unequivocal ReA are not identified in PubMed. On the other hand, extremely rare infectious agents, such as *Cyclospora cayetanensis*, *Entamoeba hartmanni*, *Vibrio parahaemolyticus*, *Orientia tsutsugamushi*, and *Rickettsia conorii*, were identified as causative agents for ReA in case reports and therefore are included as an update to the list

Table 2 Rare infectious agents implicated to cause ReA [modified from 11, 24, 25] (see supplement for additional references reporting microbial products in the joint and HLA-B27 positivity)

Entry site	Microbial agents	Microbial products in the joint	HLA-B 27 positive
Urogenital tract	<i>Gardnerella vaginalis</i>	ND	Positive
	<i>Human immunodeficiency virus</i>	Virus isolated in one patient	Positive in Caucasians
	<i>Mycoplasma genitalium/hominis/orale</i>	DNA, coinfections	Single case
	<i>Neisseria gonorrhoea</i> *	DNA	No
	<i>Ureaplasma urealyticum</i>	DNA, coinfections	No
Gastrointestinal tract	<i>Blastocytosis</i> *	ND	Single case
	<i>Clostridium difficile</i>	ND	Yes
	<i>Cyclospora cayetanensis</i> *	ND	No
	<i>Echerichia coli</i>	ND	Some cases
	<i>Hafnia alvei</i>	ND	No
	<i>Helicobacter pylori</i>	ND	Yes
	<i>Microsporidia</i>	Antigens, DNA, culture positive	Single case
	<i>Strongyloides stercoralis</i> *	Larva and antigen found in SM (one case)	Single case
	<i>Tropheryma whippelii</i> **	DNA, rRNA, culture positive	Some cases
Amoebae	<i>Vibrio parahaemolyticus</i>	ND	ND
	<i>Cryptosporidium</i>	ND	No
	<i>Entamoeba histolytica</i> *	Culture positive in one case	No
	<i>Entamoeba hartmanni</i> *	ND	Single case
Respiratory tract	<i>Giardia lamblia</i> *	ND	Some cases
	β -haemolytic <i>Streptococci</i>	ND	Some cases
	<i>Mycobacterium tuberculosis</i> *	65 kDa mycobacterial heat shock protein reactive T-cells	Some cases
	<i>Mycoplasma pneumoniae</i>	ND	Some cases
Other (skin, soft tissue)	<i>Neisseria meningitidis</i>	Immune complexes	Single case
	<i>Bartonella henselae</i>	ND	No
	<i>Borrelia burgdorferi</i> **	DNA	No
	<i>Brucella abortus/mellitensis</i>	Culture negative by definition	No
	<i>Calmette-Guerin Bacillus</i>	<i>Mycobacteri bovis</i> culture positive in one case	Yes
	<i>Coxiella burnetii</i>	ND	ND
	<i>Leptospira</i>	ND	ND
	<i>Orientia tsutsugamushi</i> *	ND	ND
	<i>Propionibacterium acnes</i>	Culture positive	Single case
	<i>Pseudomonas aeruginosa</i>	DNA	No
	<i>Rickettsia conorii</i> *	Immune complexes	No
	<i>Rickettsia rickettsii</i> *	Culture negative (single case)	Single case
	<i>Staphylococcus aureus</i>	ND	Some cases
	<i>Staphylococcus epidermidis</i>	ND	Single case
	<i>Staphylococcus haemolyticus</i>	ND	Single case
<i>Staphylococcus lugdunensis</i>	ND	ND	
Vaccination	Hepatitis B	ND	Two cases
	Influenza	ND	Single case
	Measles plus mumps	ND	ND
	Tetanus	ND	Positive
	Typhoid	ND	No

*Effective antimicrobial therapy for ReA documented in case reports

**Effective antimicrobial therapy for ReA documented in double-blind controlled studies

(Table 2; for references see supplement to Table 2). Finally, causative agents sensitive to antimicrobial therapy with efficacy to treat ReA are marked in Table 2 (for references see supplement to Table 2).

The list clearly shows the overlap between reactive and post-infectious arthritis, in that different arthritides with and without detection of microbial products in the joint are included together under the label ReA. In addition to bacteria, viruses, protozoa, amoeba, helminths, and vaccinations are listed as triggers for ReA. Regardless of the controversy relating to differentiation between the two forms of arthritis, a distinction is rarely made in clinical practice or in publications in cases of clinical similarities of joint manifestation. Moreover, infections with *Tropheryma whippelii*, *Borrelia burgdorferi*, *Neisseria gonorrhoea*, and some protozoa have therapeutic implications due to antimicrobial therapy. Recent publications thus have extended our knowledge about rare causative agents of ReA.

Urogenital Infections

A recent case report from Japan describes chronic ReA in a patient associated with chronic asymptomatic prostatitis caused by *Neisseria meningitidis* [27]. The patient had several features of ReA, including positive HLA-B27, asymmetric chronic arthritis in the lower extremities, enthesitis, and persistent urinary tract infection. Contrast-enhanced CT scans demonstrated enhanced lesions in the peripheral zone of the prostate. Culture of urine taken after prostate massage revealed *Neisseria meningitidis*. The critical lesson from this case is that in a patient with suspected ReA, it is important to look for possible unusual sites of infection, even if the infection is asymptomatic.

Gastrointestinal Infections

Clostridium difficile colitis is less often recognized as a cause of ReA. A recent report described a 58-year-old HLA-B27 positive woman with complaints of non-bloody watery diarrhoea, abdominal pain for the past 1 week, and right knee pain starting 1 day prior [28]. The patient had recently used antibiotics for a respiratory tract infection and was found to be positive for *Clostridium difficile* toxin in stool. ReA secondary to *Clostridium difficile* colitis was diagnosed, treatment with oral vancomycin and an anti-inflammatory was initiated, and the patient had complete resolution of symptoms. This case illustrates the importance to test for *Clostridium difficile* toxin in undifferentiated arthritis patients under the appropriate circumstances. It may be useful to remember the diagnostic criteria for ReA associated with *Clostridium difficile* infection proposed by Birnbaum et al. which include the following: (i) evidence of aseptic synovitis (confirmed by culture) developing during or immediately after colitis, (ii) presence of toxins

produced by *Clostridium difficile* in stool samples, and (iii) absence of other causes of colitis and arthritis [29].

Using a prospective research design, Tuompo et al. at the University of Helsinki and Helsinki University Hospital, Finland, evaluated the association between acquisition of diarrhoeagenic *Escherichia coli* (DeC) and development of ReA and other reactive musculoskeletal symptoms among international travellers [30]. ReA was defined as development of synovitis (swelling accompanied by pain and/or painful movement) in a previously asymptomatic joint within 2 months after gastrointestinal symptoms. Of 151 patients with only DeC infection, and excluding other pathogens, four (2.6%) had ReA, two (1.3%) reactive tendinitis, and three (2.0%) reactive arthralgia. ReA was mostly mild, and all patients with ReA were negative for HLA-B27. Pathogens involved were identified only because of participation in this study; travellers mostly do not seek medical care for mild travellers' diarrhoea symptoms. Antibiotic treatment of travellers' diarrhoea did not prevent development of musculoskeletal symptoms.

With regard to rheumatic manifestations following *E. coli* infection, it is important to remember the recent report of ReA from post-urogenital *E. coli* infection [31]. In this report, a 54-year-old Bangladeshi woman presented with the clinical picture of ReA following an episode of an *E. coli* positive urinary tract infection 2 weeks prior to acute right hip joint arthritis onset. Laboratory testing revealed that she was HLA-B27 negative but strongly positive for rheumatoid factor as well as anti-CCP antibody. Symptoms improved significantly within 5 days and with treatment using intramuscular steroid injection in addition to analgesia (NSAIDs and paracetamol). However, further follow-up of this patient is required to assess if she is at risk of developing overt clinical features of rheumatoid arthritis.

The diagnosis of post-enteric ReA is challenging given the diversity of enteric pathogens. Stool culture and serological tests may be negative at the time of diagnosis, making it impossible to identify the causal agent. Moreover, rare enteric microorganism may infrequently cause ReA. For only the second time, ReA associated with *Hafnia alvei* has been reported recently [32]. A 50-year-old man with persistent inflammatory low back pain, asymmetric oligoarthritis, and a clinical history positive for diarrhoea in the previous 3 months was diagnosed with presumptive ReA after careful exclusion of other inflammatory bowel diseases. Persistence of symptoms after treatment with a non-steroidal anti-inflammatory drug prompted a second look at the colon. Biopsy collected from the terminal ileum was cultured, and surprisingly, colonies of *Hafnia alvei*, a rod-shaped Enterobacteriaceae, were detected. Treatment with ciprofloxacin led to rapid resolution of symptoms. Although enterocolitis from *Hafnia alvei* has been reported only rarely, the culture of intestinal specimens

might be recommended in the work-up of patients with suspected post-enteric ReA.

Blastocystis is an enteric parasite that is endemic particularly in developing countries, and it has only rarely been encountered as the causative organism of ReA. A recent case report from Qatar presented the first case of ReA with urticaria caused by *Blastocystis* [33•]. The 18-year-old female patient presented after 2 weeks of diarrhoeal illness with a 3-day history of urticarial skin rash followed by arthritis affecting knees, elbows, shoulders, and ankles in addition to small joints of the right hand, and tenosynovitis of both the Achilles tendons. She was found to have *Blastocystis* by the stool microscopy and received metronidazole with a short course of NSAIDs and steroids leading to complete resolution of her skin and joint symptoms. Thus, especially in endemic areas, it is important to consider organisms other than the classical ones as a trigger for ReA. A recent study of patients having unexplained rheumatic pain attending the rheumatology and rehabilitation outpatient clinic in Suez Canal University Hospital reported the frequency of intestinal parasitic infection fulfilling the criteria for parasitic rheumatism, which is often published under the term ReA [34]. The results of examination of stool samples showed that 50 of 107 patients with unexplained rheumatic pain had a parasitic infection. *Cryptosporidium* infection was the most common (48%), followed by *Cyclospora cayetanensis* (32%), *Giardia lamblia* (24%), *Blastocystis hominis* (20%), and *Entamoeba histolytica* (8%). Parasitic rheumatism was diagnosed in 16 of the 50 patients (32%) most commonly due to *Giardia* infection, followed by *Cryptosporidium*, *Cyclospora cayetanensis*, *Entamoeba histolytica/dispar*, and *Strongyloides stercoralis*.

Respiratory Infections

Poststreptococcal ReA (PSRA) is associated with prior group A, β -hemolytic streptococcal infection. Distinguishing PSRA from acute rheumatic fever (ARF) can be challenging. For that reason, Chun and Kingsbury reviewed the diagnostic criteria for PSRA, the pertinent features of the 2015 ARF diagnostic guideline from the American Heart Association, and the major characteristics that differentiate PSRA from ARF [35].

Tuberculosis is an important public health problem and is a re-emerging disease, particularly in underdeveloped countries. Thus, several cases of ReA induced by active extra-articular tuberculosis (Poncet disease) have been reported in recent years. Sood et al. in New Delhi, India, described 7 patients who presented primarily with polyarthritis and fever and who developed pulmonary, pleural, or nodal tuberculosis later in the course of disease [36]. Polyarthritis resolved and did not recur in all the patients after the institution of antitubercular treatment comprised of isoniazid, rifampicin, pyrazinamide, and ethambutol for the first 2 months, followed by isoniazid and rifampicin for next 4–5 months. Another case report, also

from India, presented 5 patients with diagnosis of Poncet's disease and examined the performance of diagnostic criteria suggested by Sharma et al. [37, 38•]. All the patients with Poncet's disease had a definite diagnosis as per these criteria, illustrating their utility in routine clinical practise. The majority (4/5) of the patients were subsequently diagnosed and responded to anti-tuberculous therapy. In the other patient, a diagnosis of atypical seropositive rheumatoid arthritis or pseudo Poncet's disease was established on follow-up. Calado et al. recently reported cutaneous tuberculosis, a rare extrapulmonary manifestation of tuberculosis, associated with reactive Poncet arthritis which showed improvement of the clinical and skin condition after appropriate treatment [39]. Lastly, a case report from Japan described a patient with Poncet disease who was successfully treated with a TNF inhibitor after sufficient antitubercular treatment [40].

The association between ReA and acute *Mycoplasma pneumoniae* infection has been reported sporadically, mainly in children [41]. A recent case report described a 30-year-old Greek patient who was HLA-B27 positive and who presented with acute *Mycoplasma pneumoniae* infection complicated by ReA and asymmetric proximal myopathy; this had progressed to chronic spondyloarthritis [42]. This previously healthy man presented to an emergency department with fever, sore throat, progressively worsening bilateral lower limb weakness, and asymmetric oligoarthritis. Diagnosis was based on a positive polymerase chain reaction test for *Mycoplasma pneumoniae* using template prepared from blood and cerebrospinal fluid, and magnetic resonance imaging findings that suggested sacroiliitis. The infection was successfully treated with a 14-day course of doxycycline, and the patient was discharged without neurological symptoms. The arthritis was treated with naproxen and corticosteroids; it improved initially but later progressed to chronic spondyloarthritis. This case exemplifies the fact that extrapulmonary manifestations of *Mycoplasma pneumoniae* can occur even in the complete absence of respiratory symptoms. Diagnosis of unusual complications relating to such infections, including ReA, requires a high level of clinical suspicion and extensive investigation. Diagnosis of *Mycoplasma pneumoniae* infections is challenging. Current diagnostic modalities include various direct PCR assays, serology, and culture [43]. The gold standard for serological diagnosis is a fourfold change in antibody titres over time; IgM antibody titres rise earlier than do IgG antibodies.

Other Infections, Including Skin and Soft Tissue

ReA induced by intravesicular injection of the attenuated *Mycobacterium bovis* bacillus Calmette-Guerin (BCG) is a rare but well-known complication of non-muscle-invasive bladder cancer therapy. Cheung et al. published a unique case describing the management of repeated BCG induction which followed BCG-induced Reiter syndrome in the primary

induction series; this occurred after a 16-year disease-free interval [44]. Following the third dose, the patient developed ReA with worsening dysuria, fever, diffuse enthesitis, episcleritis, and arthritis of both knees, both ankles, left wrist, and left temporomandibular joint. The fourth instillation of BCG was delayed by 2 weeks, and the ReA was managed with steroid injections and oral non-steroidal anti-inflammatory drugs. The decision was made to give the final induction doses as scheduled. After completing his induction BCG, the rheumatologist took a more active approach to managing his arthritis, and the patient was started on oral sulfasalazine (1500 mg twice daily) and prednisone (7.5 mg daily). On this regimen, his symptoms completely resolved. Although more research is required, this case demonstrates that repeat induction is an option in the appropriate patient setting, assuming risk and benefit assessment, shared decision-making, and active rheumatologist involvement. Another recent case report of an HLA-B27 positive patient with ReA following intravesical BCG instillation illustrates that symptoms of arthritis resolved completely after a 1-year progressively reduced corticosteroid treatment [45]. Ultrasonographic findings of synovitis in both wrists, together with wrist flexor tenosynovitis, wrist extensor tenosynovitis, and also enthesitis of the flexor carpi radialis tendon, supported the diagnosis of ReA induced by intravesical BCG therapy for bladder cancer in a Japanese patient who was HLA-B27 negative but B35 positive [46]. Slouma et al. report as ReA the case of a 24-year-old Tunisian man, HLA-B27 positive, developing after the ninth BCG instillation inflammatory back pain and with evolution to an axial spondyloarthritis diagnosed 9 years later [47]. This would be the first case report presuming BCG induced axial spondyloarthritis, although one cannot exclude other intermittent asymptomatic infections as causatives for the late development of spondyloarthritis.

Several tick-borne rickettsial organisms can trigger ReA (Table 2). Redford et al. reported a case in which *Rickettsia rickettsii*, acquired on a camping trip, precipitated a flare of peripheral arthritis and episcleritis in a 45-year-old female; this patient had a 19-year history HLA-B27 positive spondyloarthritis which was well controlled for 4 years on anti-tumour necrosis factor-alpha (anti-TNF) therapy (certolizumab pegol 400 mg subcutaneously every 4 weeks) [48]. The patient had a 14-day course of doxycycline, which led to complete resolution of symptoms and resumption of her certolizumab therapy.

Evidence for Rare Infectious Agents Implicated in the Causation of Reactive Arthritis

Evidence for the causation of the organisms listed in Table 2 in ReA is extremely diverse, varying between single case reports, e.g. for *Hafnia alvei* [32], and comprehensive literature

reviews, e.g. for *Clostridium difficile* [49]. Diagnosis is based on the clinical history of an arthritis following an extra-articular infection, verified by testing for the causative agent (positive culture at the site of infection and/or serum antibacterial antibodies) but also includes arthritis following vaccination. Diagnostic criteria from the Third International Workshop on Reactive Arthritis and the criteria published by Pacheco-Tena et al. both mention only clinical diarrhoea or urethritis as the preceding infections [50, 51]. Thus, respiratory infections and vaccination are not included in the available criteria. Pacheco-Tena et al. add to their diagnostic criteria bacterial identification by peripheral blood or synovial lymphocyte proliferation, and/or synovial fluid or tissue immunofluorescence bacterial antigens or DNA or RNA detection, but these investigations are only rarely performed for the microbial agents listed in Table 2 [51]. Siala et al. conducted studies to detect bacterial DNA present in synovial tissue and synovial fluid, respectively, of Tunisian patients with ReA and other arthritides using broad-range bacterial PCR; the assay targeted a 1400-bp fragment from the 16S rRNA gene followed by cloning and sequencing the entire 16S rDNA from a wide variety of bacterial species [52, 53]. Characterization of the DNA sequences in all patients revealed a wide spectrum of commensal and environmental organisms not known to date to be present in human infections, not known to be present in inflamed joints of arthritis patients, and not known to trigger ReA. Therefore, the results of these and earlier studies with highly sensitive broad-range PCR [c.f. [53] indicate that arthritic joints are not sterile, and that the role of microorganisms triggering ReA requires further investigation.

A major problem exists in relation to the inclusion of arthritides induced by, e.g. *Borrelia burgdorferi*, *Neisseria gonorrhoeae*, and *Tropheryma whippelii*. The infection and rheumatic manifestations are treatable with antimicrobial medication despite negative culture results in the joint. Unexplained seronegative peripheral arthritis should have culture and/or PCR tests for these infectious agents whenever possible, including using the appropriate sample such as blood, stool, urine, skin biopsy, duodenal biopsy, saliva, joint fluid, and/or synovial biopsy [c.f. 34, 54–57].. Although the arthritides indicated above were formerly termed ReA and are included within the spectrum of ReA in reviews, it is important to mark the therapeutic difference given in clinical practice and the overlap to infectious arthritis.

Thus, the boundary between septic arthritis and ReA is characterized neither by the fact that the instigating bacteria are present in the joint or distant from the joint, nor by the fact that these organisms may or may not be intracellular; rather, that boundary may be characterized by the replicative or non-replicative form of these germs. The term “septic arthritis” might define situations in which the bacteria proliferate in the joint, whereas the term “reactive arthritis” should be used

to define situations in which inflammation is perpetuated by living, but non-replicative, bacteria [58].

New Infectious Agents Implicated in the Causation of Reactive Arthritis

ReA has been described only infrequently in association with *Staphylococcus aureus*, the coagulase-negative staphylococci *Staphylococcus epidermidis*, and *Staphylococcus haemolyticus* (for references see supplement to Table 2). A recent case report presented ReA in a 51-year-old male undergoing chemotherapy for pancreatic cancer who presented with joint pain and fevers. He was found to have blood culture and urine culture positive for *Staphylococcus lugdunensis* [59]. Transthoracic and transesophageal echocardiograms were negative for endocarditis. The likely source of *Staphylococcus lugdunensis* bacteremia was an indwelling catheter. Arthrocentesis from one large joint revealed culture-negative inflammatory synovitis. This case illustrates that a possible systemic manifestation of *Staphylococcus lugdunensis* bacteremia, in addition to the more common endocarditis, can also include ReA.

Orthobiologic injections, for example the placenta- and umbilical cord-derived Wharton's jelly, are currently being harvested and sold by companies as an off-the-shelf "stem cell" injection for conditions including back pain and osteoarthritis. For example, a 36-year-old male was injected with Wharton's jelly for low back pain, and within 24 h he developed fevers, chills, polyarthritis, and Achilles tendon enthesitis [60]. Infectious disease work-up was negative. Inflammatory markers were elevated, and he was positive for HLA-B27 antigen. Initial treatment included methylprednisolone and sulfasalazine. This example highlights the unknown dangers of these allogenic injections, and physicians should remain cautious about their use until further study and regulation can ensure patient safety.

Rothia mucilaginosa, also known as *Stomatococcus mucilaginosus* or *Micrococcus pneumoniae*, is a Gram-positive coccus that is part of the normal microbiota of the oropharynx and upper respiratory tract and is considered a non-pathogenic bacterium in healthy individuals. In one report, a 79-year-old diabetic man who presented with a 1-month history of polyarthralgia involving the shoulder and hip joints was initially suspected of having polymyalgia rheumatica [61]. Gallium-67 scintigraphy revealed a marked uptake in tendon attachments around the shoulders and hips bilaterally, which is usually typical for polymyalgia rheumatica. Pharyngeal bacterial culture was repeated twice, with both cultures positive for *Rothia mucilaginosa* susceptible to ampicillin. Ampicillin treatment was initiated at a dose of 750 mg/day for 3 months, leading to resolution of all clinical symptoms, and with no relapse over a 1-year follow-up, supporting the diagnosis of ReA. This unusual case has been interpreted to mean that an uncommon

organism may cause ReA in individuals at risk for infections, such as those with diabetes, and that clinicians should avoid a misdiagnosis of seronegative rheumatic diseases, such as polymyalgia rheumatica. However, that clinical manifestation is extremely rare in ReA and in the scintigraphy typical for polymyalgia; hence, the conclusion is questionable.

With the advent of the SARS-CoV-2 pandemic, several cases of acute arthritis following this viral infection were reported and classified as ReA (Table 3) [62–69]. The first review published in October 2020 as preprint discussed whether SARS-CoV-2 can trigger ReA [70]. The question arises whether COVID-19 virus-associated arthritis should be classified as ReA, as we also have discussed for *Chikungunya virus* and *Parvovirus*. Nevertheless, we provide here a complete review of relevant publications through the end of 2020.

The arthritis manifests from a few days up to 21 days after infection and from COVID-19 symptom onset, respectively. Joint involvement is oligoarticular, which is typical for ReA. Enthesitis of the Achilles tendon and psoriatic lesions consistent with spondyloarthritis have also been observed [62, 66]. Extra-articular involvement of palpable purpura of both calves was seen in one HLA-B27 positive patient [67]. HLA-B27 is otherwise negative, although this has been investigated in only one case. Synovial fluid examination with reverse transcriptase (RT)-PCR for SARS-CoV-2, investigated in two cases, was negative [64, 65]. In one case, negative viral cultures for SARS-CoV-2 were reported [65]. Of note, the clinical significance of the synovial fluid cultures and RT-PCR results is currently unknown, and the report highlights an unmet need in relation to SARS-CoV-2 ReA diagnosis [71]. The arthritis resolved spontaneously on day 27 in one patient. In the other patients, the arthritis was managed with non-steroidal anti-inflammatory drugs and intra-articular corticosteroid injection.

Importantly, four cases of acute arthritis developed during COVID-19 admissions have been reported, all due to crystal-proven flares (gout and calcium pyrophosphate disease) [72]. Therefore, during the SARS-CoV-2 pandemic, it remains essential to check every case of acute arthritis by polarized microscopy since acute illnesses, including infections, are well-established risk factors for gout and pseudogout flares [73].

Synovial Pathogenesis

Given an ever-widening array of organisms implicated in the etiology of ReA, the critical issue becomes: what is/are the pathogenic mechanism(s) underlying disease induction? Does one common process produce the arthritis regardless of initiating organism; does some small number of related processes exist to accomplish disease induction regardless of infecting organism, or are pathogenesis and disease induction differentially and individually specified by each such organism?

Table 3 Case reports communicating clinical features and management of patients with ReA during COVID-19 admission

Author	[62]	[63]	[64]	[65]	[66]	[67]	[68]	[69]
Age/gender Time from COVID-19 symptom onset to arthritis	50s/male 21 days	37/female 12 days	57/male 15 days	47/male No COVID-19 symptoms, 4 days after exposure to coronavirus disease COVID-19 cases	30/male 14 days	65/female 10 days after cessation of all COVID-19-rela- ted symptoms	34/male 16 days	39/female 3 weeks
Involved joints	Bilateral arthritis in his ankles, mild enthesitis in right Achilles tendon.	Pain and swelling in the right hand. MRI showed tendinitis of multiple extensor tendons	Left wrist, the right shoulder and the bilateral knees	Right knee pain and swelling, and pain at his glans penis.	Right elbow, psoriatic lesions on the extensor surface of both elbows and groin suggestive	Symmetric polyarthritis of ankles, wrists and knee joints; palpable purpura of both calves	Swelling, severe pain and tenderness in his right knee	Tenderness in the PIP joint of the second and third fingers and the DIP joint of the fifth finger of the right hand. Tenderness in the second PIP joint and tenderness, swelling, and decreased range of motion in the DIP joint of the left-hand fifth finger.
HLA-B27 SF characteristics	Negative Mild inflammatory fluid without monosodium urate and calcium pyrophos- phate crystals	ND ND	ND No crystals	ND 120 mL of turbid yellow fluid, for which no crystals were seen.	Negative ND	Positive ND	ND ND	ND ND
Synovial fluid RT-PCR for SARS-COVI- D-19	ND	ND	Negative	Synovial fluid PCR negative, viral SARS-COVID-19 negative	ND	ND	ND	ND
Arthritis management	NSAIDs and intra-articular corticosteroid injection	Volaren gel, neuronin, and oral dilatuid as needed.	No treatment	Etoricoxib, intra-articular triamcinolone into the knee joint 1 week later when the effusion recurred.	NSAIDs for arthritis and topical steroids for skin lesions	Prednisolone	NSAID and intra articular steroid	celecoxib for two weeks
Outcome	Treatment of moderate improvement. No further follow-up	4 weeks follow-up. Pain and tenderness to the hand and wrist had improved, however, she still complained of tenderness to the dorsal aspect of the wrist and hand, especially to the finger joints	The arthritis resolved spontaneously on day 27	No information	Remission after six weeks	All clinical symptoms and CRP levels immediately regressed after initiating prednisolone	Symptoms of arthritis resolved completely within next 10 days.	pain and swelling disappeared after several days

CRP, c-reactive protein; MRI, magnetic resonance imaging; NSAIDs, non-steroidal anti-inflammatory drugs; ND, not done; PMN, polymorphonuclear; RT-PCR, reverse transcriptase PCR; SARS-COVID-19, severe acute respiratory syndrome coronavirus 19; DIP, distal interphalangeal joint; PIP, proximal interphalangeal joint

For the well-established and well-studied primary etiologic agents, including *Chlamydia trachomatis* and the various Gram-negative gastrointestinal pathogens, a reasonably good understanding exists concerning mechanisms of joint pathogenesis in ReA. In the case of arthritis occurring post-*C. trachomatis* genital infection, studies have indicated that the organism is transported to the joint intact in infected monocyte/macrophages, and it establishes itself within those cells in synovial tissue, there eliciting synovial inflammation. The pathogen is in an unusual metabolic state during transport and establishment in synovial tissue, referred to as “persistence”, which is characterized in part by an unusual panel of gene expression and partial antibiotic refractoriness. Destruction of *Chlamydiae* in monocyte/macrophages is aborted due to as yet poorly understood aspects of pathogen-host cell interaction at the molecular level [see e.g. [74–76]]. This is in contrast to infecting gastrointestinal pathogens, which do not reach the joint in a viable and intact state. Rather, studies have demonstrated that parts of the infecting organism that include “arthritogenic peptides” reach the synovium, where it is thought that they are displayed by a subset of HLA-B27 allelic products to elicit an inflammatory response; at least in part, that response may occur via molecular mimicry, thus initiating autoimmunity [74, 77]; see also below]. Several other explanations for pathogenesis have been put forward in the HLA-B27 context, including heavy chain homodimer formation and HLA-B27 misfolding. It should be noted, however, that the rate of HLA-B27 positivity in ReA patients is lower than that in patients with ankylosing spondylitis (30–50% vs 80% or more, respectively). Thus, other mechanisms for joint inflammation and pathogenesis must exist; one of these may well relate to the overall composition and alteration of gut microbiota in some patients [74 and see below].

Further, it has been clear for many years that ReA can be one of several possible sequelae to inflammatory bowel disease (IBD). In these cases, the arthritis and other morbidities have been linked to the structure of some specific forms of lipooligosaccharides from the infecting organism which interact with the host innate immune system [e.g. 78]. Multiple levels of interactions between the host and infecting pathogen are emerging as critical to disease induction. Recent in silico studies have indicated, for example, that the Na/H antiporter and kynureninase, among several other proteins, are important targets for such interaction; these and similar kinds of studies will provide critical guidance for researchers to design experimental systems for dissection of those detailed interactions, and for elucidation of pathogenesis mechanisms elicited by novel agents given in previous sections [79].

Other etiologic agents for ReA are not among the Gram-negative bacteria as are those discussed above, but are rather Gram-positive, the Group A *Streptococci*, the *Staphylococci*, *Rothia* spp., and others. Interestingly, post-*Streptococcal* ReA has been recognized and reported for many years, while

arthritis related to these others has been reported only rarely [e.g. 80, 81]. It seems probable from several studies that ReA in this context is a function of the known and well-characterized pathogenic proteins produced by these bacteria. Further, and importantly, it is likely that joint pathogenesis elicited by the more recently identified bacterial and eukaryotic pathogens introduced above, such as *H. alvei*, *C. difficile*, and *Blastocystis*, will follow that same pattern [see 82, 83]. Much more research will be required to sort out details of synovial inflammation and pathogenesis by these newly identified agents. It will be of significant interest to follow details of such studies, including whether patients with ReA apparently caused by these organisms conform to relatively well-established patterns for disease elicited by other, classic pathogens, such as that of HLA-B27 positivity, or whether new and expanded categories of characteristics and pathogenic mechanisms will be defined.

Arthritis following respiratory infection is an interesting issue, especially with respect to whether the organisms eliciting it are, in fact, present in the joint and intact to engender disease. ReA following extra-articular tuberculosis, as mentioned above, has been reported a number of times, and it is treatable with standard antituberculosis treatment; it is not clear from most of the reports whether *Mycobacterium tuberculosis* or some of its components are in fact identifiable in synovial fluid or tissues. In cases of arthritis following pulmonary infection with *Mycoplasma pneumoniae*, nucleic acids from the organism have been identified by PCR in blood samples and, as mentioned above, from CSF, suggesting that the organism or its parts are likely to be present in the affected joint [42]. We have studied the ReA that can follow pulmonary infection with *Chlamydia pneumoniae* [e.g. 84]. As with studies of *C. trachomatis*-induced ReA, we identified the organism within the joint in *C. pneumoniae*-induced arthritis, and we found production of messengers for multiple proinflammatory mediators there as well. The organism is viable and metabolically active within the joint, as with *C. trachomatis* [75, 85]. Thus, the mechanism(s) eliciting joint inflammation and pathogenesis in the context of *C. pneumoniae* infection is/are congruent to that/those characteristic of *C. trachomatis* at that site.

Importantly, a number of recent studies have indicated that the epidemiology of ReA has been changing. In part, this alteration in disease distribution and diagnosis results from evolving, and somewhat inconsistent, diagnostic criteria [e.g. 18, 86]. It may also result, in some cases, from a general lack of recognition of this arthritis in affected patients [19, 87]. However, in large part this change in disease distribution must result from recognition of the increasing array of etiologic agents underlying the disease, including viruses. Reports of arthritis in patients with current or previous viral infections have appeared from time to time in the literature [see 88] for discussion]. With the advent of the current viral pandemic, reports of patients with inflammatory arthritis following

SARS-CoV-2 infection have proliferated [e.g. 62, 89, 90]. Most such reports simply describe the case of one or a few patients, and the treatments administered with outcomes, but most do not include PCR or other testing to assess presence of the virus or its parts in the synovium. Thus, determination of pathogenic mechanisms must await further research. One reasonable possibility, though, centres on the question of molecular mimicry. In one recent study of alphavirus-mediated arthritis, the authors performed an extensive *in silico* analysis to ask whether molecular mimicry post-viral infection could elucidate a possible autoimmune reaction to engender the arthritis; the answer provided indicated that it was indeed possible [91]. Much more study will be required to assess disease-inducing mechanisms in post-viral contexts, as well as in situations in which other pathogens elicit inflammatory arthritis.

Conclusion

In view of the large spectrum of causative agents, it is clear that diagnostic consideration must include the entire diversity of post-infectious arthritis termed ReA. The diagnostic procedure should not be restricted to the well-known HLA-B27-associated group of ReA, but must also cover the large number of more rare forms of arthritis following infections and vaccinations, as well as newly described members of the group of ReA summarized in this review. This increased array of pathogens must support increased research into the panoply of mechanisms involved in disease elicitation, and elucidation of those mechanisms will in turn inform the treatment and management of ReA in all contexts.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s11926-021-01018-6>.

Declarations

Conflict of Interest The authors declare no competing interests.

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causes of ReA to strains with less chance of producing an immune response (less arthritogenic) but this is speculative.

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