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ORIGINAL ARTICLE

Evolving patterns of reactive arthritis

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Abstract

Objective To characterize rheumatologists' perspectives on evolving trends of reactive arthritis (ReA).

Methods After ethics approval, 548 members of the Canadian Rheumatology Association were surveyed with 37 questions covering their demographic information, subspecialty, level of experience, practice setting and opinions on prevalence, treatment, and causes of ReA. Results were analyzed with descriptive statistics.

Results Ninety-seven responded to the survey (18% response rate); 66 fully completed it. Nearly half of respondents believed that the incidence of ReA is declining and causes of ReA may be changing. Physicians reported that most of the ReA cases in their practices were caused by an unknown organism, sexually transmitted, or gastrointestinal infection. Full triad ReA increased the chance of recurrence according to their impressions. Common investigations in ReA included inflammatory markers, HLA-B27, chlamydia and gonorrhea testing, stool cultures, synovial fluid analyses, SI joint imaging. ReA treatment included NSAIDs, intra-articular corticosteroid injections, and DMARDs. Two-thirds said they used TNF alpha inhibitors in chronic ReA occasionally or more frequently.

Conclusion ReA may be decreasing in frequency and severity in Canada. Changes could be due to less food borne illness, cleaner water, or more rapid treatment of sexually transmitted infections. The cause is often unknown in clinical practice.

Key Points
- *Reactive arthritis (ReA) is likely decreasing in prevalence and severity.*
- *Patients with classic trial of arthritis, urethritis, and conjunctivitis are more likely to have recurrent and/or chronic ReA.*
- *The causal organisms are often not detected and seem to be changing over time.*

Keywords Evolving trends · Reactive arthritis · Reiter's syndrome · Survey · Treatment

Introduction

Reactive arthritis (ReA) is defined as inflammatory arthritis developing after a bacterial infection (especially gastrointestinal or genitourinary) and can have other features (conjunctivitis, urethritis, keratoderma blennorrhagicum, circinate balanitis, oral ulcers, nail changes, ulcerative vulvitis) [1, 2]. ReA is within the category of undifferentiated spondyloarthritis. It is thought to be more common in young men: the ratio of affected men to women is a 3:1 [1, 2]. However, there is evidence that many cases of ReA in women are not diagnosed [3]. ReA may occur with a classic triad of conjunctivitis, urethritis, and asymmetric oligoarthritis. Full triad ReA arthritis was previously named Reiter's syndrome.

ReA occurs possibly due to molecular mimicry after an initial infection of the genitourinary, gastrointestinal, or less likely respiratory tract [2]. Though the exact mechanism is unknown, it is believed that microbial antigens may inappropriately interact with self-proteins and trigger a sustained

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immune response [4]. *Shigella*, *Salmonella*, *Yersinia*, and *Chlamydia* infections are organisms historically reported in ReA [3]. Though synovial fluid cultures of affected joints are often negative for these bacteria, their nucleic acids and proteins have been found in the synovium of affected patients [5–9]. HLA B27, which is involved in antigen presentation to lymphocytes, is linked to ReA [10–13]. Patients with HLA-B27 are 50 times more likely to develop ReA after an infection [4]. ReA seems to be increased in patients positive for human immunodeficiency virus (HIV) [14]. ReA is a diagnosis of exclusion if the infectious cause is not apparent [15]. ReA should however still be considered in the absence of infectious symptoms as triggering infections may be asymptomatic in a quarter of affected individuals [16].

The worldwide prevalence of ReA in adults is cited as 1/1000 [3], although this varies geographically. For example, higher prevalence is noted in Scandinavian countries with greater HLA B27 positivity and lower prevalence in regions with less HLA B27 frequency such as Indonesia, Philippines, and Malaysia [17, 18]. ReA is rare in children [19, 20]. In developed countries ReA prevalence is likely decreasing [21]. Recurrent or chronic ReA is reported to be as high as 50–60% of adults with ReA [22]. The frequency of recurrent full triad ReA is unknown. The tests ordered in patients thought to have ReA are not standardized. We sought to understand rheumatologists' perspectives on ReA and whether it is changing over time. We attempt to capture the perceived evolving prevalence, investigations and treatment in ReA.

Methods

This study was approved by the Canadian SHIELD Ethics Review Board No. 17-10-003. No patients participated in our study; therefore, informed patient consent was not required. Members of the Canadian Rheumatology Association (CRA) were surveyed via email (548 in total of whom 433 are practicing rheumatologists either adult or pediatric, and the others are trainees and emeritus status). Results were by physician report and were not verified by chart data. The survey is in the supplement. Physicians were asked 37 questions about demographic information, experience level, and practice setting, the prevalence of acute, recurrent, chronic and full triad ReA in their practice, frequency of ReA manifestations, causes of ReA in their practice, and their relative frequency, tests they order to investigate suspected ReA, and treatment for ReA. Overall, their perspective on epidemiological changes in the incidence, severity and causes of ReA were explored.

Inclusion criteria Physicians could participate in the study if they were members of the Canadian Rheumatology Association (CRA). Participants could be either trained rheumatologists or trainees (adult and pediatric).

Data were summarized as frequency and means, box plots, and bar charts and histograms were constructed.

Results

Ninety-seven responded (18% response) but 66 completed the entire survey (Table 1). No demographic influences on physician answers based on gender ($p = 0.4$), practice setting ($p = 0.4$), or years in practice ($p = 0.5$) were found. Forty-seven per cent of respondents believed that the incidence of ReA is declining, compared to 6% who thought it is increasing. Respondents tended to believe that the common causes may be changing (39% agreed/strongly agreed). The mean number of ReA patients seen ever and over the last year for practicing adult rheumatologists was 43.5 ± 60.0 and 5.0 ± 4.9 respectively and was 29.0 ± 2.1 and 3.0 ± 2.1 for practicing pediatric rheumatologists (Table 2). Acute, chronic, and recurrent ReA were all thought to have similar frequencies in their practices (Fig. 1a).

In terms of presentation, asymmetric oligoarthritis occurred in the majority of ReA cases seen by participants (78%) (Fig. 1c). The full triad ReA occurred in approximately 21% of ReA cases, and patients with conjunctivitis or urethritis were very likely to exhibit the rest of the triad (conjunctivitis, urethritis, and arthritis) (Fig. 1c). Similarly, patients with recurrent ReA were more likely to exhibit the full triad (43%) vs. acute or chronic (14%) (Fig. 1b).

Table 1 Socio-demographic characteristics of respondents ($N = 97$)

Characteristic		*N*	%
Sex			
	Male	43	44.3
	Female	54	55.7
Practice			
	Adult rheumatology	69	71.1
	Pediatric rheumatology	13	13.4
	Trainee	15	15.5
Years in practice			
	Under 5 years	30	31.6
	Between 6 and 10 years	13	13.7
	Between 11 and 15 years	9	9.5
	Between 16 and 20 years	9	9.5
	Between 21 and 25 years	7	7.4
	Over 25 years	27	28.4
Practice setting			
	Community	31	32.0
	University	57	58.8
	Both	9	9.3

Table 2 Physician reported frequency of reactive arthritis (mean ± SD)

Acute ReA		
	Cases this year	1.8 ± 2.5
	Total cases ever	13.1 ± 21.6
Recurrent ReA		
	Cases this year	1.9 ± 3.3
	Total cases ever	14.1 ± 30.3
Chronic ReA		
	Cases this year	2.3 ± 3.6
	Total cases ever	14.2 ± 31.0

Trainees were excluded in this analysis as they saw fewer cases of ReA

Physicians reported the percentage of their patients that exhibited full triad ReA, recurrent ReA, and recurrent full triad ReA. From this, the relative risk of recurrence given full triad ReA was calculated to be 1.70 times more common than the overall ReA population. The distribution generated from these responses is shown in Fig. 1c.

Participants reported that the infectious cause of ReA was found in only 35% of cases. Unidentified infectious organisms were the most common cause of ReA in their practice, followed by sexually transmitted diseases (18%) and gastrointestinal (14%) infections (Fig. 2). Chlamydia testing was frequently ordered in suspected ReA as was HLA B27, stool cultures, and joint aspirations (Fig. 3). Imaging was ordered by 39% of respondents with SI joint imaging ordered by 21%, X-rays of the affected joints by 15%, and other imaging by 7.5% (Fig. 3).

Physicians showed a strong preference towards treatment of ReA with NSAIDs (frequently or always used by 97% of respondents) (Fig. 4). The next most common therapies were intra-articular corticosteroid injections (65% frequently or always used) and disease-modifying anti-rheumatic drugs (DMARDs) (45% frequently or always used). Two-thirds said they used TNF alpha inhibitors at least occasionally.

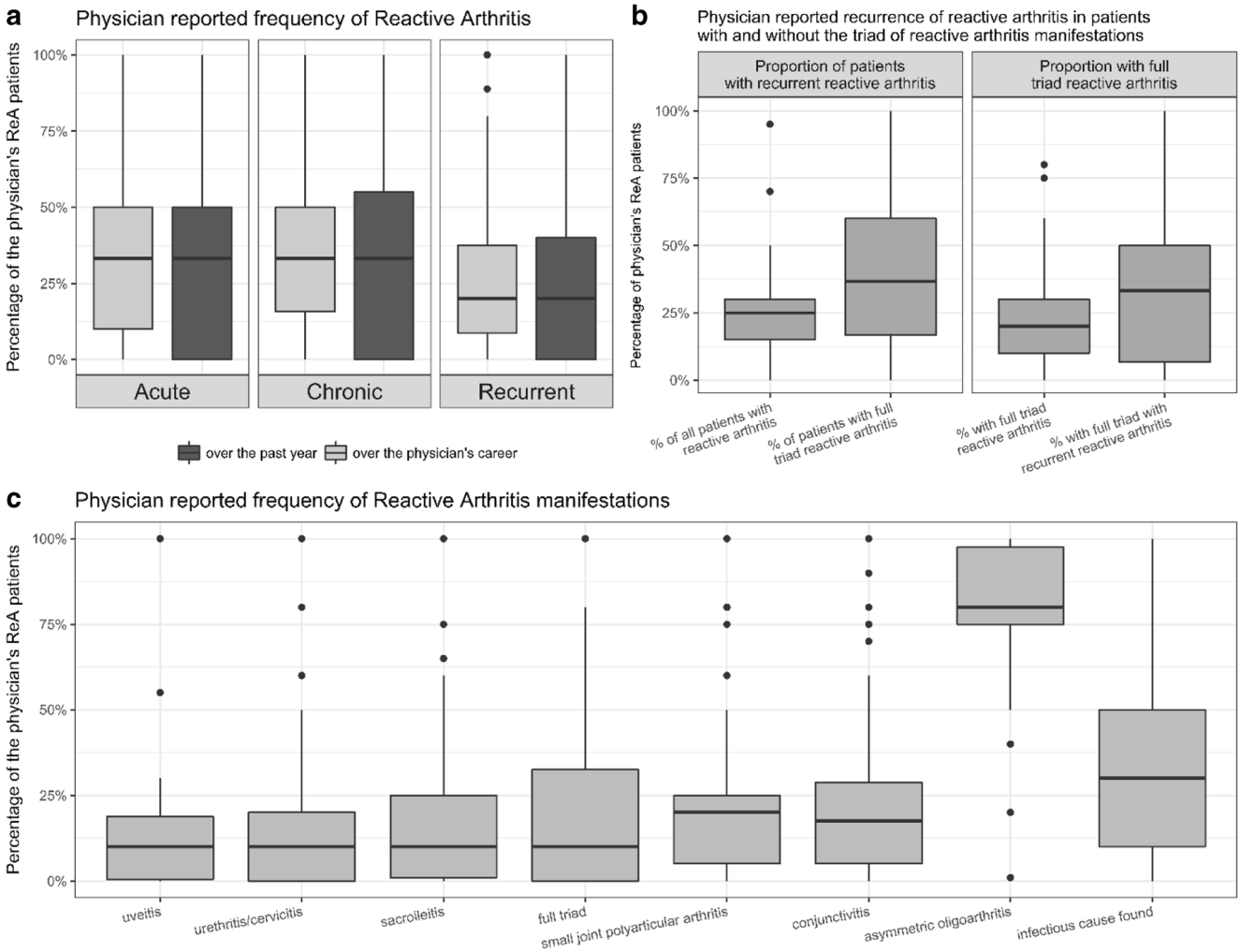

Fig. 1 Characteristics of reactive arthritis (ReA). **a** Prevalence of ReA durations in physicians' practices over the past year and their entire career. **b** Physician reported recurrence of reactive arthritis in patients with and without the triad of reactive arthritis manifestations in their practices. **c** Physician reported frequency of ReA manifestations in their practices

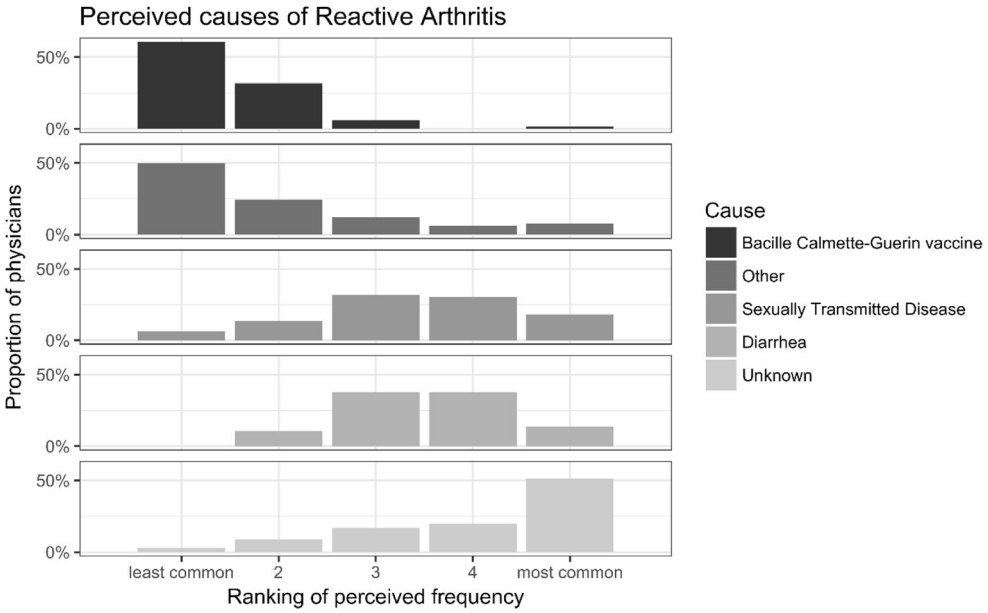

Fig. 2 Perceived cases of reactive arthritis

Discussion

This study shows perceptions on the relative frequency of ReA over time seen by rheumatologists in Canada and that it may be decreasing. Usually, the organism is not identified, and the full trial of signs is more likely to accompany recurrent or chronic ReA. Whether there are changes in severe ReA cases is unknown. ReA has been described in older literature, but less has been published with respect to trends in manifestations over time [22–26]. According to respondents, ReA may be decreasing in severity (less than full triad of symptoms and less chronic ReA) and its causes may be changing. We

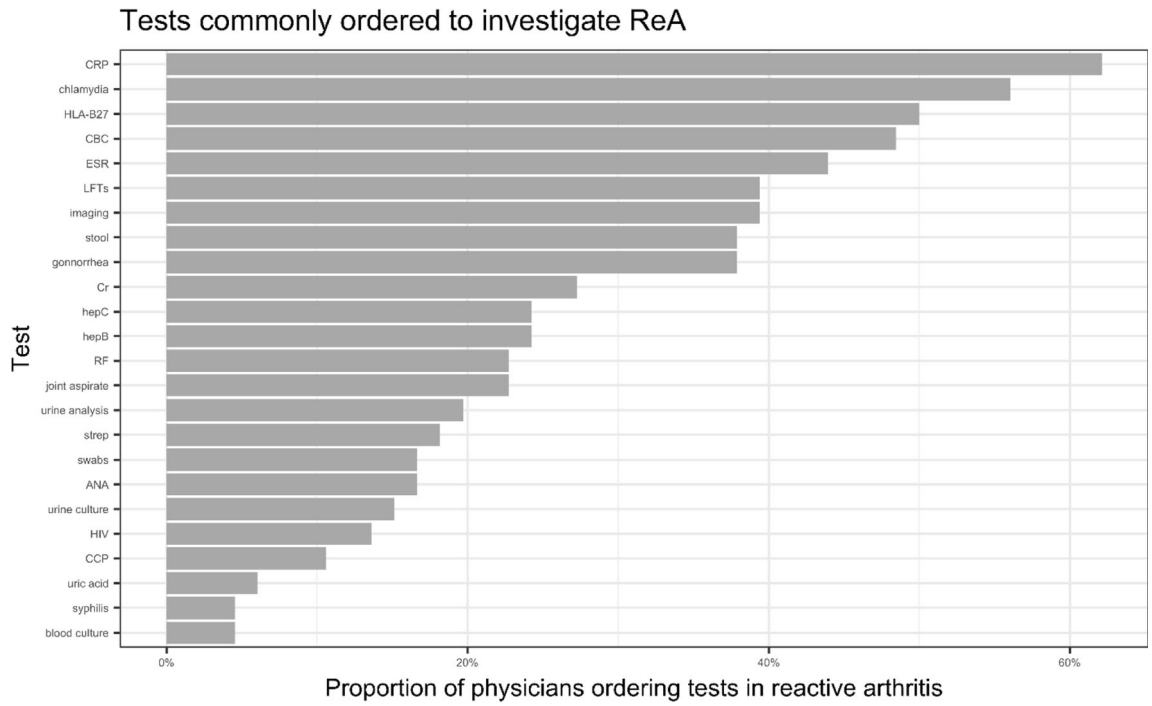

Fig. 3 Most commonly ordered investigations for suspected reactive arthritis. Tests were included in the figure if ordered by three or more physicians. CRP C-, reactive protein; chlamydia, chlamydia testing; HLA-B27, human leukocyte antigen B27; CBC, complete blood count; ESR, erythrocyte sedimentation rate; LTFs, liver function tests; imaging, any imaging modality of any joint; stool, stool culture; gonorrhea, gonorrhea testing; Cr, creatinine; hepC, hepatitis C; hepB, hepatitis B; RF, rheumatoid factor, joint aspirate, joint aspirate culture; strep, streptococcal testing; swabs, swab cultures; ANA, antinuclear antibodies; HIV, human immunodeficiency virus; CCP, cyclic citrullinated peptide; syphilis, syphilis testing

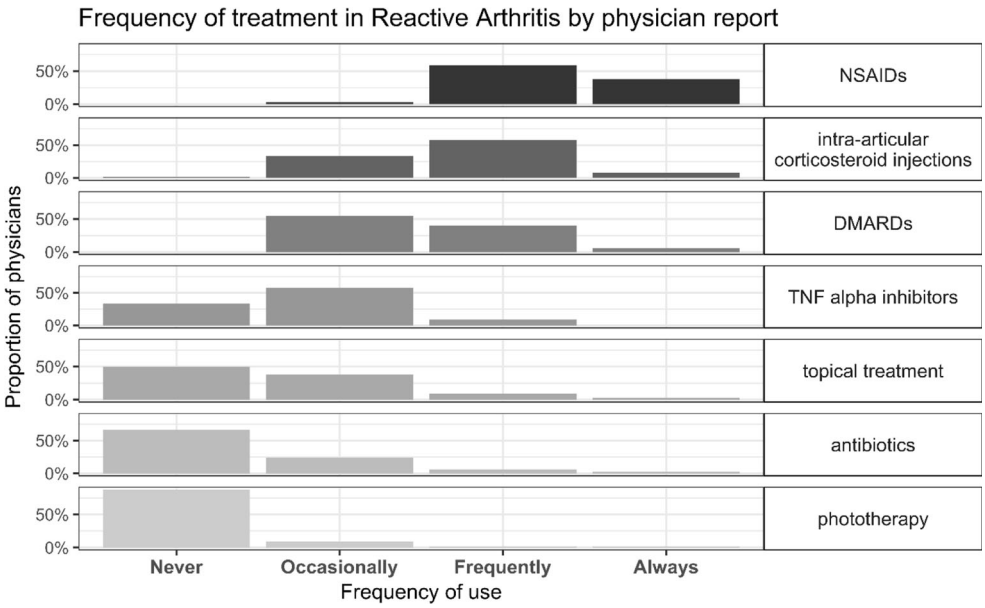

Fig. 4 Frequency of treatment in reactive arthritis by physician report. TNF alpha inhibitors, tumor necrosis factor alpha inhibitors; NSAIDS, non-steroidal anti-inflammatory drugs; DMARDS, disease-modifying antirheumatic drugs

speculate that epidemiologic changes could be attributed to a decrease in food borne illness, increased availability of clean water, increased sanitation, and more rapid treatment of STIs [27–29]. Reactive arthritis with other features (conjunctivitis, urethritis, and skin such as circinate balanitis, keratoderma blennorrhagicum) are possibly more likely to be recurrent as there is more severe/widespread involvement so the ability to be predisposed genetically with such a reaction in the future is higher. Chronicity would also be more likely due to the severity of the immune response.

This study has limitations including perceptions of rheumatologists which have not been verified by billing codes or chart audits. The response rate was only 18% so the generalizability of these insights is unknown. However, there were not differences between respondents with respect to type of practice and experience. There were more respondents from academic centers than community (as the distribution of the members of the Canadian Rheumatology Association is approximately a 50/50 split). This could be a bias towards more severe cases and/or a special interest in ReA. However, it is likely that mild cases of ReA may not be referred to rheumatologists as they are not necessarily chronic and are self-limited. We did not ask about co-infection with HIV or whether ReA in patients with HIV is changing.

In terms of treatment, the strong preference towards treatment of ReA with NSAIDs by respondents (frequently or always used by 97%) is in line with the standard of therapy for seronegative spondyloarthropathies [3]. Almost half of respondents frequently or always used DMARDs and two-thirds TNF alpha inhibitors at least occasionally.

Some data are available in the literature regarding DMARDs and biologics in the treatment of ReA [3].

Culture negative infections are perceived to be the most common causes of ReA in Canadian rheumatology practices. Improved detection and treatment of bacterial STIs and better food safety could account for the perceived decrease in ReA prevalence [27–30]. However, recent data show that STI rates (especially among young men) have greatly increased in the last 5 years [31–33]. This recent surge of STI infections may be attributed to modern dating culture and shifts in attitude towards public health [30, 34]. As a result, there may be an increase in the prevalence of ReA in the future if the infections are arthritogenic organisms and especially if identification and treatment of STIs is delayed. Antibiotics were not used often in the respondents as treatment despite some positive data suggesting they may be helpful and other data where they are not beneficial beyond usual treatment of the infectious precipitator [35, 36].

Conclusions

ReA may be decreasing in frequency and severity (less than full triad of symptoms and less chronic ReA) in Canada. Changes could be due to less food borne illness, cleaner water, more rapid treatment of STIs, or mutations of common infectious causes of ReA to strains with less chance of producing an immune response (less arthritogenic) but this is speculative. We found evidence that Canadian rheumatologists perceive the full triad to be linked to chronic and recurrent ReA.

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Compliance with ethical standards

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Ethics This study was approved by the Canadian SHIELD Ethics Review Board # 17-10-003.

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