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Leader

Reactive or infectious arthritis

Why reactive arthritis?

A role for bacterial infection in the aetiology of inflammatory arthritis has been suspected for many years. Yet over that relatively long period of time only a few acute or chronic arthritides have been unequivocally linked to an infectious agent; these include septic arthritis, rheumatic fever, and, more recently, Lyme arthritis. The term reactive arthritis was first introduced to describe the association between *Yersinia enterocolitica* infection and arthritis, and it was intended to differentiate this form of acute, non-suppurative arthritis, which is characterised by negative joint culture, from infectious, purulent arthritis; the differentiation was meant to suggest an underlying sterile immune mediated pathomechanism.¹ A few years later, immediately after discovery of the association between HLA-B27 and ankylosing spondylitis and Reiter's syndrome, the term reactive arthritis was also related to this genetic marker; at this time the term was more strictly applied to the HLA-B27 associated reactive arthritides, following infections with enterobacteria and chlamydia.² This concept has been widely recognised and accepted. However, non-HLA-B27 associated arthritides, such as Lyme disease induced by *Borrelia burgdorferi*, Neisseria gonorrhoeae induced reactive arthritis, post-streptococcal reactive arthritis, and rheumatic fever are viewed presently as reactive arthritides (see table 1 for the spectrum of bacterial species triggering reactive arthritis). This inclusion is based on the observation that these arthritides also develop after a primary extra-articular infection, and that despite negative culture results, the organisms can be detected in the joint (for example, *Borrelia*,⁷ *Neisseria*⁹).

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

Are genetic associations a prerequisite for reactive arthritis?

Today, association with HLA-B27 should no longer be considered intrinsic to the definition of reactive arthritis, as possession of the allele is not a prerequisite for the induction of reactive arthritis, even after chlamydial or enterobacterial infection. However, HLA-B27 has been identified as a genetic factor predisposing people with

chlamydia induced or enterobacteria induced reactive arthritis to a more severe peripheral arthritis and involvement of the spine and sacroiliac joint.¹²

Bacterially induced disease must always result from host-bacteria interaction. Indeed, different genetic associations in the context of sequelae induced by differing bacterial species are well known for other diseases.¹³ The fact that Lyme disease and rheumatic fever are not associated with HLA-B27, but rather with MHC class II molecules (HLA-DR2 and DR4), is not an argument against viewing these diseases as reactive arthritides; rather, it underlines the need for better analysis of the specific details of host-bacteria interaction. Indeed, it is well known that even at different sites of primary extra-articular infection, the same organism can lead to different genetic associations and different clinical pictures for the arthritis. For example, in one study, *Bacillus Calmette-Guerin* (BCG) given intra-dermally to increase anti-tumour immune responses induced a polyarticular, symmetrical arthritis without axial involvement resembling rheumatoid arthritis. No association with HLA-B27 was found, and women were affected more often than were men. In contrast, the same organism when instilled intra-vesically induced an oligoarticular,

Table 1 Bacteria triggering reactive arthritis—manifestations at the entry site (see references 3–11,23,29,34)

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

*Reactive arthritis triggering bacteria associated with HLA-B27.

Primary infection	Infection at the extra-articular entry site		
Dissemination	Uptake by mononuclear cells (?) or dendritic cells (?) = distribution of the organisms from the site of entry into the joint		
Intra-articular persistent infection	Viable, metabolically active but non-culturable organisms persist in synovial tissue		
Arthritis	Bacterial persistence	-> Host cell activation	-> Release of cytokines and prostaglandins
		-> LPS	-> Release of cytokines
		-> hsp-expression	-> DTH-reaction (CD4+ T cells)
		-> Antigen processing/MHC I	-> γ/δ T cells -> CD8+ cytotoxic T cells

Figure 1 Aetiopathogenesis of reactive arthritis.

asymmetrical arthritis mainly affecting lower limbs with sacroiliac involvement; in this case, men showed a preponderance of disease. This "reactive arthritis"-like disease was linked to HLA-B27 and also showed ocular manifestations.⁴

Importantly, in reactive arthritis several different, distantly or unrelated bacterial species all can cause similar clinical syndromes after primary extra-articular infection. With the intra-articular detection of the triggering organism, diagnosis based on aetiology is available. Different genetic associations and differences in the clinical spectrum should stimulate research to define the precise mechanisms responsible for disease development.

Pathogenic mechanisms of host-bacteria interactions

After detection of antigens from various bacterial species known to trigger reactive arthritis (for example, *Chlamydia trachomatis*, *Salmonella enteritidis*, *Yersinia enterocolitica*) in synovial fluid and tissue, the hypothetical process of pathogenesis was viewed primarily as a sterile immune mediated synovitis with dead bacteria, or non-proliferating antigens, present in the joint tissue. However, recent studies have demonstrated that biopsy material from the synovial membrane of patients with chlamydia induced arthritis often contain intact chlamydial DNA and RNA, even as late as 12 years after the onset of disease.^{14 15} Furthermore, morphologically atypical, but intact appearing, chlamydial organisms were found in phagosomes of monocytes, and to a lesser extent synovial fibroblasts.^{15 16} These observations suggested that *Chlamydia trachomatis* can persist in the joint in a viable state. The demonstration of short lived messenger RNAs (mRNA) and primary ribosomal RNA transcripts (rRNA) from the same organism indicated that synovial Chlamydias are indeed both viable and metabolically active.⁶ The implication of these demonstrations of intracellular, metabolically active but non-culturable Chlamydias in the synovium of reactive arthritis patients is that the organism is arrested at some point in its life cycle, preventing the generation of new infectious Chlamydias.

A major issue relating to persistent chlamydial infection of the joint concerns the means by which the organism reaches the synovium from the urogenital system, the usual site of primary infection. Intracellular Chlamydias have been demonstrated within monocytes isolated from synovial fluid and from the synovial membrane of patients with chlamydia induced arthritis.^{15 16} Recently, the detection of chlamydial DNA by polymerase chain reaction (PCR) in peripheral blood leucocytes was reported in two patients with chlamydia induced arthritis.¹⁷ These observations suggest that monocytes may be involved as the vehicle transporting Chlamydias from the genital epithelium to the synovium. Theoretically it can be

speculated that Chlamydias persist mainly in the urogenital tract, and that the demonstration of viable Chlamydias in the joint rather reflects continuous or discontinuous dissemination via circulation than persisting infection of the joint. Future research has to investigate this hypothesis.

The question of whether enteric bacteria also reach the joint in the form of intact, viable bacteria or only as antigenic material has not been clarified unequivocally as yet. The finding of bacterial antigens in peripheral blood cells of patients with yersinia induced arthritis as much as several years after onset of disease supports the view of persisting infection in the gastrointestinal tract, with subsequent distribution to the joint.¹⁸ Along the same line, studies of patients with yersinia induced arthritis demonstrated the presence of yersinia protein antigens, but not DNA, in the joint.^{19 20} In contrast with these findings, DNA from this organism was detected recently in synovial fluid from one patient with reactive arthritis.²¹ Moreover, in biopsy specimens from patients with yersinia induced arthritis the structure of bacteria observed by immunofluorescence microscopy had the appearance of complete organisms.²² DNA from *Salmonella* and *Campylobacter jejuni* has been shown in synovial fluid.²³ With respect to PCR analyses of the enteric bacteria, major concern relates to the use of synovial fluid rather than synovial tissue, as well as to the lack of validation of the sensitivity of the preparation method and PCR systems used.^{24 25} Both these may decrease significantly the ability to detect DNA from the respective species. Further studies are necessary to define the exact metabolic condition of bacteria associated with post-enteric reactive arthritis. Continued synthesis of the bacterial antigens required to drive the synovial inflammatory process is probably required for maintenance of that process (fig 1). In principle, appropriate antigens can be synthesised by bacteria persisting within the joint, or they may derive from the site of primary infection with consequent distribution of antigenic material to the joint.

Terminology and classification

In view of the above new insights into the persistence of bacterial antigens and organisms in inflamed joints, we argue that it is necessary to appropriately amend the nomenclature, terminology, and classification for reactive arthritis. The strict nosological distinction between infective, infectious, septic, suppurative, and purulent arthritides on the one hand and non-septic, aseptic, sterile, reactive arthritis on the other must be revisited. We suggest here that the term "infectious" should be applied only to conditions and disease manifestations that fulfil the classic Koch's postulate. Similarly, the terms "infective" and "purulent" or "suppurative" should be reserved to inflammatory arthritides in which bacterial organisms can be grown by culture from joint samples. The differentiation

		Infectious arthritis	Infection reactive arthritis	Infection triggered reactive arthritis
Koch's postulates	Initiating extra-articular infectious disease	+	+	+
	Isolation of the bacteria at the entry site	+	+	+
	Positive culture from the joint	+	–/(+)	–
	Transfer of the microbe to a susceptible host	+	–/(+)	–/(+)
Intra-articular				
	-Bacteria viable non-culturable	–	+	–/(?)
	-Bacterial antigens	+	+	+/-*
	-Bacterial DNA/RNS	+	+	(+)
Defective or over-reacting immune response		–/+	+	+
Arthritis sensitive to antibiotics		+	(+)	–(?)

Figure 2 Hypothetical model of infectious, infection reactive and infection triggered reactive arthritis. * Bacterial antigens have not (yet) been detected intra-articularly in rheumatic fever.

between “septic” and “reactive” arthritis does not focus on primary pathogenic differences.²⁶ “Septic” arthritis implies not only suppurative arthritis but that, after primary infection at the entry site or target organ, viable bacteria are disseminated via bacteraemia to the joint, leading to “infective arthritis”. For certain reactive arthritides, such as chlamydia or borrelia induced reactive arthritis, bacteraemia and dissemination of viable organisms into the joint after primary extra-articular infection also has been described. A precise definition of reactive arthritis should include two types of reactive arthritis: (a) “infection reactive” arthritis, characterised by the intra-articular persistence of viable though non-culturable bacteria, and (b) “infection triggered reactive arthritis”. In the latter, bacterial antigens derived from viable bacteria elsewhere in the body are disseminated to the joints, causing an immune mediated arthritis. This distinction may be based on our current level of understanding rather than on a real difference. Future research will be necessary to elucidate whether chlamydia associated reactive arthritis and the post-enteric reactive arthritides do, in fact, differ in light of these definitions. We add here that our personal view is that the terms “non-septic” and “aseptic” should be avoided in the characterisation of reactive arthritis. We prefer instead indications such as “non-infectious”, “non-culturable” or “non-productive” to describe the fact, that at least at present bacteria cannot be cultured consistently by routine methods from joint samples of patients with reactive arthritides.

The recently proposed term “slow bacterial infection” may be appropriate to describe the relation between the survival/persistence of bacterial agents and the host immune response in reactive arthritis.^{27–29} In the context of chlamydial infection, the term “persistence” has been coined to indicate “a longterm association between *Chlamydiae* and their host cells, in which these organisms remain in a viable but culture negative state”.²⁸ For Chlamydia slow bacterial infection of the joint is defined by the intra-articular demonstration of metabolically active chlamydial organisms and the fact that despite negative culture results different morphological forms of Chlamydiae persist in the joint, suggesting that Chlamydiae undergo some kind of growth.^{15 29} This special state of the host-bacteria interaction does not exclude the possibility of an intermittent or slow replication of the microorganism. “Persistent infection” was defined as “the absence of overt chlamydial growth, suggestive of the existence of *Chlamy-*

diae in an altered state distinct from their typical intracellular morphological forms”.

In the future, rheumatologists should recognise properly the wide diversity of host-microbe interactions underlying the various forms of arthritis, and they should be familiar with the appropriate nomenclature and terminology. Figure 2 summarise our present knowledge concerning the relation between infection and arthritis, and it modifies earlier classifications given by Dumonde *et al*³⁰ and Toivanen.¹¹ The two types of reactive arthritides proposed are intended to refer to, and be based upon, our present understanding; however, they must be viewed as rather preliminary, given the probability of future important and new insights into the basic pathogenic interactions of host and bacteria. Today, reactive arthritis can be defined tentatively as an immune mediated synovitis resulting from slow bacterial infections and showing intra-articular persistence of viable, non-culturable bacteria and/or immunogenic bacterial antigens synthesised by metabolically active bacteria residing in the joint and/or elsewhere in the body.

Research agenda and perspectives

One of the most important questions in reactive arthritis is why only 1–10% of people infected with *Chlamydia*, *Yersinia*, *Salmonella* or other microorganisms known to trigger reactive arthritis actually develop the disease.³¹ In the future, host genetic factors that predispose infected persons to disease development must be elucidated. Furthermore, both the wide spectrum of disease (acute versus chronic disease), and the fact that some people do harbour chlamydia in their joints without any clinical signs of arthritis,³² underline the need for a better understanding of host-parasite interaction.

International standardisation of diagnostic methods, such as PCR, to detect persistent intra-articular organisms is, of course, urgently needed. DNA amplification by universal PCR and nucleic acid sequence based identification of microorganisms directly from the clinical specimens will probably become the diagnostic standards of the future to elucidate potential bacterial causes of arthritis.

A better understanding of host-bacteria interaction and the host factors predisposing to disease will broaden the horizon of potential specific treatments for reactive arthritis. Combination antibiotic treatment may be one way to eliminate persisting organisms. Local or systemic corticosteroid treatment, as well as immunosuppressive therapy, both of which are in current and successful use,

theoretically bear two potential positive effects; that is, they may reactivate bacterial growth allowing susceptibility to antibacterial treatment, and they may ameliorate potential harmful effects by further reducing immune responses that clearly are unable to eliminate the organism. Imbalances in the synovial cytokine milieu in reactive arthritis are increasingly understood.³³ Specific therapeutic modulations to upregulate the protective and downregulate the disease inducing/maintaining effects of cytokines are needed.

The aims for the future are that early diagnosis and treatment of extra-articular infection, reduction of primary infection by vaccination (for example, against *Borrelia*), standardised and highly sensitive diagnosis of the specific intra-articular infecting organism(s), and specific treatments based on better knowledge of the host-bacteria interaction will enable the rheumatologist to prevent and cure these common rheumatic diseases. Rheumatologists currently successfully treat diseases of unknown cause. In reactive arthritis, the bacterial cause is established. Let us tackle it.

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JENS G KUIPERS
LARS KÖHLER
HENNING ZEIDLER

Division of Rheumatology, Medical School, 30623 Hannover, Germany

Correspondence to: Professor Dr H Zeidler, Division of Rheumatology, OE 6850, Medizinische Hochschule Hannover, 30623 Hannover, Germany.

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