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HLA-B27-Associated Reactive Arthritis: Pathogenetic and Clinical Considerations

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INTRODUCTION

Reactive arthritis (ReA) is defined as a sterile synovitis developing after a distant infection, usually in the genitourinary or gastrointestinal tract. The detection of microbial components (microbial DNA and RNA) in the joints of patients with ReA has led to the reconsideration of this definition (59). Currently, ReA is better defined as an immune-mediated synovitis resulting from slow bacterial infections and showing intra-articular persistence of viable nonculturable bacteria and/or immunogenetic bacterial antigens synthesized by metabolically active bacteria residing in the joint and/or elsewhere in the body (104, 204). A classification into HLA-B27-associated and nonassociated forms has also been proposed (28, 95, 206). Post-streptococcal, Lyme, and viral arthritis are HLA-B27 nonassociated and should be described as distinct entities under the general heading of "infection-related arthritides."

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This article focuses on HLA-B27-associated ReA. This form of ReA belongs to the group of spondyloarthropathies (SpA), is triggered by bacteria (which enter the body through the mucosal surfaces) from the genera *Campylobacter*, *Chlamydia*, *Salmonella*, *Shigella*, and *Yersinia*, and is clinically associated with oligoarthritis of the lower limbs and sometimes with urethritis and conjunctivitis (203, 210).

HISTORICAL CONSIDERATIONS

Hippocrates in the fourth century B.C. was probably the first to link the presence of arthritis and infection in the genitourinary tract (7, 95, 122) when he noted that "A youth does not suffer from gout until after sexual intercourse," gout meaning acute arthritis at that time. Interestingly, historical records concerning Christopher Columbus indicate that he suffered from arthritis associated with eye inflammation. If this, however, was "the first case of ReA in the old world," it remains a point of further discussion (1, 6, 72, 77).

Sir Benjamin Brodie, in 1818, was the first to describe the classic triad of urethritis, arthritis, and conjunctivitis in a series of five patients (31, 225). Gonococcal identification by Neisser in 1879 facilitated the differential diagnosis of patients with nongonococcal arthritis from the arthritis of disseminated gonococcal infection (1, 95).

On the other hand, the association of arthritis and dysentery or diarrhea was first recognized in the late 1600s (22, 224). Paronen et al. at the end of the second world war reported their experience with a large outbreak (more than 150,000 individuals) of dysentery secondary to *Shigella* (151). Of these, 344 (<1%) individuals developed arthritis, and four cases were associated with conjunctivitis. In 1916, several reports of this association were published almost simultaneously in Germany and France. Fiessinger and Leroy described four cases of urethritis, arthritis, conjunctivitis, and diarrhea, which they named the "oculo-urethro-synovial" syndrome (51). This clinical association is still known in France as the Fiessinger and Leroy syndrome. In Germany, Hans Conrad Reiter reported a similar clinical syndrome in a young German soldier and suggested a spirochetal infection as the triggering agent (156); however, he did not provide confirmation studies. To his credit, however, ReA secondary to the Lyme disease spirochete was recently reported from the same geographic area in which Reiter's patient resided (218).

The eponym Reiter's syndrome became widely adopted in the literature following its first description in the American medical literature by Walter Bauer and Efrain Engelman (18). In recent years, the Nazi past of Hans Reiter has come to light (216). He was responsible for involuntary sterilization, euthanasia, and medical experiments that killed thousands of concentration camp prisoners (60). Based on these considerations and Reiter's ethical background, several authors and groups including The Spondylitic Association of America, a patient advocacy group that represents people with this clinical syndrome, have strongly recommended that this syndrome should be called "reactive arthritis" (218).

TABLE 1. Identification of bacteria and bacterial products in the joint by different methods[a]

Bacterium	Presence in joint of bacterial products			
	Antigens	DNA	RNA	Culture
C. trachomatis	+	+	+	±
Y. enterocolitica	+	+	ND[b]	−
Y. pseudotuberculosis	+	−	+	−
S. flexneri and *S. sonnei*	+	+	ND	−

[a] Data are from reference 175.
[b] ND, not done.

PATHOGENESIS

ReA is definitely related to an infectious disease, and multiple factors contribute to its development. Three central aspects of the pathogenesis of ReA are the presence of bacteria or bacterial products in the joint (Table 1), the bacterium-host interaction, and the local immune response directed against these bacteria. The fact that such different bacteria can induce arthritis, yet some bacterial subtypes (such as *Yersinia* O:8 or *Shigella sonnei*) in a single species do not, provides evidence that antigenicity alone does not determine the induction of arthritis. Rather, it may be a property of the ability of the bacterium to reach the joint or gain access to particular cell types and evade the host defenses (180, 230).

Based on the lack of a single hypothesis that could unify the pathogenesis of ReA and the complexity of this topic, we review the most relevant data on each of these three aspects. As an introduction to these discussions, Fig. 1 (175) summarizes the natural history of arthritogenic infections.

Evidence of *Chlamydia* in the Joints

Using a number of different techniques, it was demonstrated that *Chlamydia* is present in the joints of patients with ReA. Intact chlamydial forms have been identified by electron microscopy, and specific DNA in structures that appear to be chlamydial cells was found by in situ hybridization (14, 197), and *Chlamydia* mRNA was detected by reverse transcriptase PCR (69, 183).

Chlamydial DNA is more likely to be found in the synovial tissue than in the synovial fluid (26, 143). The difficulty in growing *Chlamydia* from joint fluid or tissue may be explained by the fact that the organism persists as intracellular reticulate bodies rather than as infectious elementary bodies. Live but noncultivable intracellular organisms may be driving the inflammation in chlamydial ReA.

The discovery of mRNA and rRNA (nucleic acids which have a half-life of minutes in tissues) of *C. trachomatis* using reverse transcriptase PCR of synovial biopsy specimens provided evidence of the occurrence of transcription and hence active multiplication of the bacteria (59). *C. trachomatis* was also found in cells of the peripheral blood but not in the serum by PCR of samples from patients with early *Chlamydia*-induced ReA (104), making it likely that monocytes (143) may be involved as the vehicle transporting chlamydiae from the genital epithelium to the synovium. Chlamydial DNA in the joints of ReA patients does not correlate with the immune response, whether measured by antibodies or by lymphocyte prolifera-

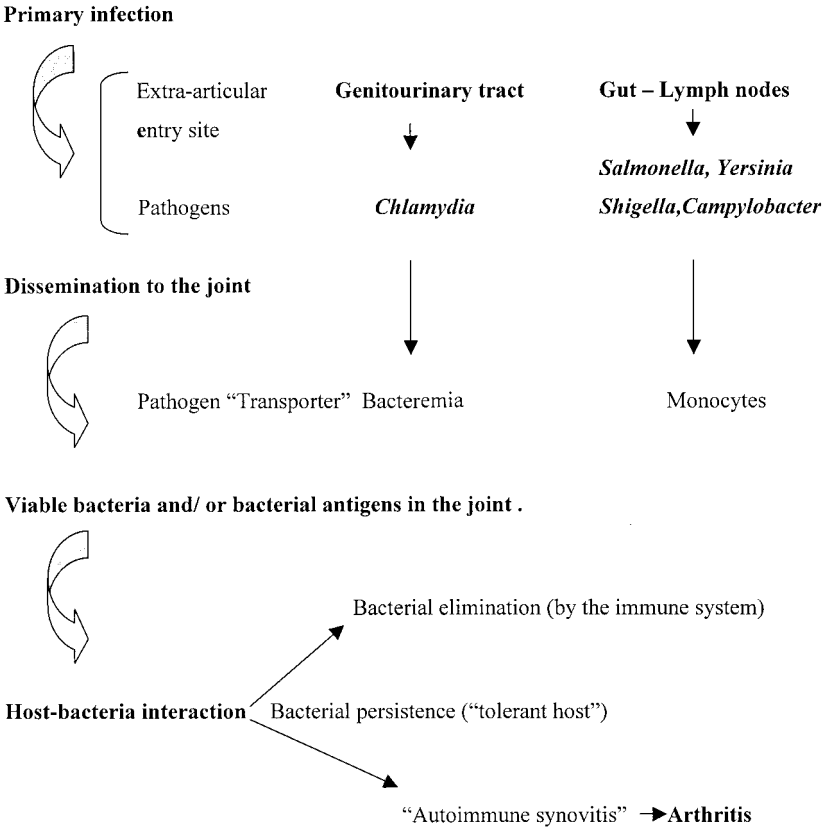

FIG. 1. Events in the natural history of the arthritogenic infection. Data are from reference 175.

tion (181). Actually, an inverse relationship between the presence of chlamydial DNA in the joint and the synovial *Chlamydia*-specific lymphocyte proliferation was found. This suggests that an impaired T-cell response might contribute to the persistence of bacteria. In synovial tissue, the transcript for Omp1, the major outer membrane protein of chlamydiae, which is the major target of the humoral immune response, was not detected, but transcripts for other chlamydial proteins, e.g., heat shock protein 60, were found (59).

Evidence of Enteric Pathogens in the Joints

Attempts to cultivate yersiniae or salmonellae from the affected joints has usually failed (62, 64, 70). DNA of *Yersinia*, *Shigella*, or *Campylobacter* has been identified in some studies, but these are few and include very few patients (175). In inflamed joints of patients with *Salmonella*-triggered ReA, no bacterial DNA was found (147).

Antigens of the enteric pathogens *Yersinia enterocolitica*, *Salmonella enterica* serovar Enteritidis, and *S. enterica* serovar Typhimurium have been identified in joints by using immunohistochemistry with samples of synovial tissue or synovial fluid (64, 70). Lipopolysaccharide LPS of *Yersinia*, *Salmonella*, *Shigella* (62, 63, 64), *Chlamydia trachomatis* (88), and the YadA protein (70) and 61-kDa heat shock protein (66) of *Yersinia* are antigens found in the joints from ReA patients. *Yersinia* lipopolysaccharide (LPS) and hsp in synovial fluid and peripheral blood cells were found for up to 4 years in ReA patients (66), which explains the fact that patients who develop ReA have long-lasting and strong immunoglobulin A responses. *Salmonella* LPS has been found in synovial tissue 2 years after the onset of infection (62), and other indirect proof of the persistence of *Salmonella* in the host is the presence for several months of antibodies at high concentrations in serum samples from patients with ReA, whereas antibody concentrations decline in salmonellosis patients without arthritis (129).

Bacterium-Host Interaction

Chlamydial ReA. *Chlamydia* enters the articular cavity during bacteraemia or within monocytes (104). Several mechanisms allows *Chlamydia* to cause persistent infection and escape from the immune system of the host. Among them, the downregulation of the expression of antigen presentation molecules, the inhibition of host cells apoptosis, and the induction of T-cell apoptosis deserve further discussion.

Chlamydia resides intracellularly in the synovial tissue (110) (rather than in the fluid [26]), displaying an aberrant morphology (irregular shape rather than the standard-size, spherical reticulate body) (143). An in vitro model showed that in the aberrant form that characterizes persistent *C. trachomatis* infection, copies of the chromosome of the bacterium accumulate in the apparent absence of subsequent cell division (19) and the expression of *omp1* (the gene encoding the major outer membrane protein [MOMP]) is attenuated during persistence. These issues help to provide some "invisibility" from immune surveillance. The upregulation of the expression of the chlamydial *hsp60* gene (which specifies a highly immuno-

genic protein) (59) is important for the inflammatory response that characterizes *Chlamydia*-associated arthritis.

Chlamydia inhibits the apoptosis of host cells by inhibiting the release of mitochondrial cytochrome *c* and also by directly engaging the death domains of the tumor necrosis factor (TNF), receptor family (48, 230). *Chlamydia*-infected monocytes induce apoptosis of autologous T lymphocytes through the release of TNF-α (88). Similarly, *Y. enterocolitica* also induces macrophage apoptosis by suppressing the activation of NF-κB, which inhibits TNF-α release. Thus, both *Chlamydia* and *Yersinia* interfere with immune cell activation of T cells and macrophages, and this may critically affect the host immune response and the resulting outcome of infection with these microorganisms (48, 162, 230).

On the other hand, *Chlamydia* directly stimulates infected host cells to upregulate proinflammatory or immunostimulatory soluble mediators (TNF-α, interleukin-6 [IL-6], IL-1, inducible nitric oxide synthase, and alpha interferon [IFN-α]) (211). If elementary bodies are taken up by macrophages/monocytes, these become activated. Alternatively, organisms may be processed by dendritic cells or other antigen-presenting cells, leading to pathogenic responses by both T and B lymphocytes. *Chlamydia* polyclonally stimulates both T and B cells in humans and experimental animals to secrete cytokines that further promote inflammatory responses in tissues (121).

Enteric ReA. In the enteric forms of ReA, the persistence of bacterial antigens may explain the appearance of an inflammatory reaction in the synovium. It is likely that these bacteria survive at an extra-articular site, in particular in the mucosal membranes of the digestive system and/or the lymphatic ganglions, and are carried to the joint by monocytes, probably in recurrent fashion (66, 101, 102). Mucosal leukocytes collected from patients with an inflammatory bowel disease (which could be extrapolated to ReA) can bind well to synovial vessels (166), and after reaching the joint, the bacterial antigens can persist in the synovium.

Yersinia and *Salmonella* can persistently infect the mucosa of the intestine and the digestive ganglions but not the synovium (66). These microbes are also present in monocytes, which may serve as a reservoir and "transporter" from extra-articular sites into the joint. A recent study investigated the mechanisms involved in the invasion, degradation, and persistence of *Yersinia* and *Salmonella* in synovial fluid (138). Infection of synovial fluid with these bacteria started with the adhesion of the bacteria to synovial cell membrane and was followed by uptake of the morphologically intact bacteria into the cells. A few hours after infection, the bacteria showed very low metabolic activity and started a process that finally led to the total disappearance of the bacterial cytosol (nucleic acid-free bacterial rods known as "ghosts").

Yersinia surface structures are critical for the adherence and internalization of these bacteria. *Yersinia* adhesin (YadA) binds specifically to joint collagens, which may contribute to their arthritogenic potential (30). The proteins necessary for *Yersinia* host invasion are not constitutively expressed. They are encoded by genes in a virulence-responsible plasmid and are designated Yops (for "*Yersinia* outer proteins") (80). These genes are activated only when the bacteria are in proximity to host cells. YopB and YopD decrease the secretion, by cultured human intestinal and cervical cell lines in vitro, of IL-8, a potent chemoattractant of polymorphonuclear leukocytes (173). The *Y. enterocolitica* virulence factors invasin, protein tyrosine phosphatase, cytotoxin, and adhesin interfere effectively with the microbicidal action of neutrophils. This could enable the extracellular survival of *Yersinia* in host tissues (162), and such persistence may permit the initiation of an inflammatory process. In addition, *Y. enterocolitica* suppresses the cellular activation of NF-κB, which inhibits TNF-α release and triggers apoptosis in macrophages (162).

A natural epitope derived from a *Yersinia* protein is presented by major histocompatibility complex MHC class I even though the microbes are found mostly extracellularly and, when seen in an intracellular compartment, remain entirely within the vacuole. Such presentation may subject the infected cell to recognition by cytotoxic T lymphocytes (168). *Y. enterocolitica*, as well as *S. enterica* serovar Typhimurium, has the ability to induce the apoptosis of macrophages, in vitro, *Yersinia* was shown to perturb dendritic cell function (167, 189), mechanisms that might be important for bacterial survival (80).

Yersinia has two envelope proteins that are cross-reactive with the thyrotropin receptor and have a mitogenic activity on B cells (231). Patients with elevated levels of anti-*Yersinia* antibodies are prone to thyroid gland disturbances (116). A structural similarity between the human thyrotropin receptor and *Y. enterocolitica* has been described and considered a possible mechanism for autoimmunity (205).

Shigella infects only digestive epithelial cells, and transportation by monocytes is highly unlikely because this bacterium rapidly kills monocytes through apoptosis. *Shigella* DNA has not been convincingly demonstrated in the joints of ReA patients, making it more likely that only pieces of bacteria are transported to the joints. It has been reported that only *Shigella* strains containing the pHS-2 plasmid are arthritogenic (180, 191). pHS-2 influences invasiveness and intracellular and intercellular movement and hence is important for the mechanism of infection.

The potential role of the commensal microflora in the development of ReA merits discussion (38). This issue is of great relevance, considering that the majority of disease-causing bacteria from the intestine may have been derived from commensals that have acquired genes from foreign sources, turning them into pathogens (68). A variety of commensal microorganisms including *Pseudomonas* spp., *Salmonella* spp., *Bacillus cereus*, and *Lactobacillus* spp. have been identified by PCR in the synovium of patients with ReA (171), and the conventional intestinal microflora plays an important role in the development of arthritis in the HLA-B27 transgenic-rat model (195). In addition, the exact role of and/or relationship between the microflora and the compromised function of the intestinal barrier needs to be established.

Bacterial Target Antigens

Arthritogenic peptides. The problem in finding immunodominant antigens shared by the ReA-inducing pathogens may be due to the heterogeneity of the T-cell population in the synovial fluid (190). The arthritogenic peptide hypothesis suggests that the arthritis is triggered by a T-cell response to specific antigenic peptides derived from the triggering bacteria and that these T cells then cross-react with self-antigen-derived

peptides (65). Certain bacteria have constituents which display strong homology to proteins of the host (e.g., YopH of *Y. pseudotuberculosis* and CD45). This molecular mimicry can give rise to tolerance of some microbes, which may thus escape from the immune system of the host. On the other hand, the mimicry may also be differently interpreted by the host, because the homology between this bacterial constituent and an antigen of the articular cavity can induce an "autoimmune" synovitis (175).

For years, an intensive search for the decisive arthritogenic antigen has been going on. Bacterial hsp60 seems to be a major target of the T-cell response in ReA, and cross-reactivity against autologous hsp60 has been discussed as a cause of autoimmunity (180). Chlamydial hsp60, the Hc1 protein (a histone), and an OMP (Omp2) were found as target antigens recognized by $CD4^+$ T cells (40). The T cells specific for hsp60 of *Chlamydia* did not cross-react with hsp60 from enterobacteria.

In *Yersinia*-induced ReA, patients have antibodies directed against a multitude of *Yersinia* antigens. *Yersinia* LPS, or YadA, seems to be essential for the induction of arthritis (180). A cationic 19-kDa urease B subunit, hsp60, and the ribosomal protein L23 of *Y. enterocolitica* O:3 were also identified as immunodominant antigens (10, 153). The urease subunit is highly conserved, and this observation lends support to the possibility that autoimmunity in reactive arthritis may be mediated by antigen mimicry between evolutionarily conserved epitopes (137). Also in *Yersinia*-triggered ReA, proteins secreted by the bacterium, including a protein with tyrosine phosphatase activity (YopH), are potent immunogens stimulating $CD4^+$ T cells within the inflamed joint (109). The pathogen-reactive T-cell clones preferentially utilize a limited set of T-cell variable gene segments, suggesting the role of superantigens (193) in the pathogenesis of ReA.

Bacterial LPS. Bacterial LPS plays an important role in the pathogenesis of ReA (128) because it contributes greatly to the virulence of the bacteria and acts to modulate the immune system. Monocytes that phagocytose *Y. enterocolitica* O:3 are a constant source of a membrane-active form of LPS in their microenvironment (226). In patients with *Salmonella*-triggered ReA, the persisting humoral immune response and intra-articular antibodies are directed primarily against LPS (130).

Intra-articular LPS are powerful macrophagic stimulators and can trigger the synthesis of proinflammatory cytokines (TNF-α, IL-1, and IL-6) through CD14-Toll-like receptor activation (208, 232). LPS also enhance lymphocyte entry into joints by their effects on the vascular endothelium, induce the synthesis of monocyte chemotactic protein 1 in human articular chondrocytes (213), enhance the secretion of the polymorphonuclear leukocyte chemotactic and activating cytokine IL-8 from chondrocytes (127), and decrease C5aR expression on monocytes (94). All these changes contribute to the recruitment of leukocytes into the synovium and lead to the persistence of mononuclear phagocytes within the inflamed synovium. LPS, together with macrophages, contributes to the degradation of cartilage matrix by collagenases and other neutral proteases secreted by chondrocytes (87). LPS also suppresses proteoglycan synthesis and induces the production of nitric oxide by chondrocytes (164). In response to LPS, monocytes produce tissue factor which is associated with thrombotic complications (226).

Bacterial DNA. Bacterial DNA, which differs from that of eukaryotes by the presence of more nonmethylated CpG motifs, can intensely stimulate monocytes/macrophages and thus could be a target antigen. Experimental intra-articular injection of bacterial DNA is sufficient to trigger arthritis in mice (42).

Host

HLA-B27. HLA-B27 is a serologic specificity that encompasses 25 glycoproteins (HLA-B*2701 to HLA-B*2725) that are also called subtypes of HLA-B27 (158). HLA-B27 is an allele of the HLA class I molecules. MHC class I molecules have as their function the presentation of endogenous peptides derived from intracellular proteins to the αβ T-cell receptor on $CD8^+$ cytotoxic T lymphocytes. In infected cells, viral peptides are bound by class I MHC molecules and are presented to the T-cell receptor on cytotoxic T lymphocytes, and the infected cell is lysed (159, 230).

A direct role of HLA-B27 makes the strongest genetic contribution to the development of SpA, although how much and how it contributes to ReA are important questions. The association of B27 and ReA is illustrated by the fact that the prevalence of disease in B27-positive individuals is five times greater than in the general population. In B27-positive relatives of patients with ReA, the prevalence is another 10 times greater (49). The generation of the HLA-B27 transgene in both rats and mice leads to the development of arthritis, which is another way of validating the role of the HLA-B27 gene in arthritis (195). In transgenic animals, susceptibility to disease is clearly related to gene copy number and level of expression of B27, and the specificity of the peptides bound to B27 appears to play an important role in the pathogenesis of arthritis.

The role of HLA-B27 may be related to its major function as a class I antigen (presenting antigenic arthritogenic peptides to cytotoxic lymphocytes) (170, 174). The arthritogenic peptide hypothesis, stating that a microbial or self-antigen is presented to $CD8^+$ T cells, has received some attention. Molecular mimicry between HLA-B27 and bacterial molecules has also been a consideration because similar amino acid sequences in HLA-B27 and *Yersinia* (194) or *Shigella* proteins have been found (109); thus, cross-reactivity could lead to tolerance and persistence of organisms.

Recently, it was found that the heavy chains of HLA-B27 possess an unpaired cystein at position 67 in the B pocket of the peptide binding groove, which may lead to the formation of unusual forms of HLA-B27, i.e., homodimers and heterodimers, which are subsequently recognized by CD4 T cells through their T-cell receptors and NK receptors (4, 5, 20, 131). Such dimers can bind peptides and apparently stimulate $CD4^+$ T cells. HC-B27 is more abundant in patients with HLA-B27-associated disease than in healthy B27 individuals. These data could explain why a class I molecule is associated with a disease driven by T-helper cells. It also explains why mice transgenic for HLA-B27 develop arthritis only when lacking β_2-microglobulin (99). β_2-Microglobulin inhibits the formation of HC-B27 by binding to monomeric B27 heavy chains (23).

A different hypothesis about the role of HLA B27 arose from the observation that HeLa cells transfected with HLA-B27 respond to in vitro bacterial invasion with signals not observed in control cells (79, 227). This could explain why

HLA-B27 cells accommodate bacterial survival differently from control cells. The explanation of the different signals could be that HLA-B27 differs from other HLA alleles in that when maturing inside the endoplasmic reticulum, the protein is folded significantly more slowly (136). Colbert et al. showed that in ReA during the antigen processing and assembly pathway in the endoplasmic reticulum, HLA-B27 has a tendency to misfold even without any β_2-microglobulin or peptide deficiency. This misfolding implicates the B pocket of the molecule and can lead to a stress response, which could increase the production of proinflammatory cytokines by activation of the NF-κB (35, 36)

Additional mechanisms have been proposed to explain the role of HLA-B27. In some genetically predisposed subjects, HLA-B27 appears to lack the ability to eliminate infected macrophages normally (92, 111), improving the intracellular survival of pathogens (183). Indeed, it has been shown that the adhesion molecules of certain bacteria (*Yersinia* and *Salmonella*) use HLA-B27 as a ligand to attach to cells of the synovial environment. The expression of most of the HLA-B27 epitopes is decreased on monocytes that have ingested *Yersinia* or *Salmonella* in vitro (93, 227). This change of expression is mostly posttranslational, although the synthesis of HLA-B27 is also decreased. Interestingly, *S. enterica* serovar Typhimurium and *Y. enterocolitica* also induce alternative splicing of the pre-mRNA of HLA-B27 with removal of the fifth exon. Because this fifth exon encodes the transmembrane domain, cell-free soluble HLA-B27 is generated (75).

In vitro the elimination (but not the uptake) of *S. enterica* serovar Enteritidis from HLA-B27-transfected U937 cells was remarkably impaired compared with that from HLA-A2 transfectants serving as controls (105). This suggests that HLA-B27 itself may influence the intracellular persistence of arthritis-triggering *Salmonella* strains within monocytes. In vivo endogenous HLA-B27-positive primary human fibroblasts did not differ from HLA-B27-negative cells in the ability to support invasion and in the persistence of *S. enterica* serovar Enteritidis (78).

The gut. The increased frequency of subclinical inflammatory lesions in the gut in patients with SpA (139) and the known association between inflammatory bowel diseases and SpA support a pathogenic link between gut inflammation and SpA that is independent of HLA-B27 (186). Animal models of SpA emphasized the role of the intestinal flora in pathogenesis. In HLA-B27 transgenic animals, both colitis and arthritis develop only in animals that have been transferred from germ-free or specific-pathogen-free conditions to normal animal facilities (196).

A suggested hypothesis is that during the acute infection in the gastrointestinal mucosa, other bacterial antigens also penetrate the destroyed epithelial layer and meet the gut-associated lymphoid tissue, leading to stimulation of the leukocytes. Lymph nodes and the gut submucosa have been suggested as potential reservoirs of arthritis-triggering bacteria, since it seems improbable that bacterial proteins could persist for long in the absence of any continuing source of infection (209). *Yersinia* structures have been shown to persist in the submucosa of the gut (73) and in lymph nodes of patients with prolonged or chronic *Yersinia* arthritis (209). Thereafter, T cells primed to local bacteria in the gut might see the same or related bacterial antigens or cross-reacting self antigens in peripheral or sacroiliac joints (45), leading to the development of the rheumatic manifestations (226).

The joints. The joints behave in many ways like part of the reticuloendothelial system and are prime sites for lodging of circulating infectious agents (169). Microbes or their components may enter the joints via blood vessels either as whole organisms that may circulate in the blood or within the cells or as a part of immune complexes (62, 172). Peripheral blood mononuclear cells that contain intracellular bacterial fragments are especially prone to bind to synovial high endothelial venules and transmigrate through the endothelial cell monolayer (101). Monocytes that have phagocytosed ReA-triggering agents can induce the expression of P-selectin on cultured endothelial cells; this molecule is important for homing to the synovium (166).

The discovery of *C. trachomatis* DNA by PCR in synovial samples from healthy volunteers and patients with osteoarthritis (OA) (171) and the simultaneous presence of RNA of numerous bacterial species in synovial samples from patients with rheumatoid arthritis (RA) or OA demonstrate that the synovium is not a sterile structure but more probably is an interfacial zone which can be colonized by bacteria originating from the environment and the endogenous flora (175). Such intra-articular microbes, depending on the characteristics of the host, may be eliminated or may provoke a synovial infection.

There are definite changes at the synovial level in ReA. Unlike rheumatoid arthritis, in which synovitis is the initial or primary lesion, the synovitis of SpA is a secondary event after enthesitis, at least in some joints (135). Arthroscopy shows that the synovial vascular pattern is typically tortuous and bushy (in contrast to RA, where the vessels are straight and branching) (155). A comparative morphometric analysis of cell apoptosis in various forms of arthritis showed no difference between ReA and other arthritides (32).

Immune Response to Bacteria

In the pathogenesis of ReA, T cells play a central role and both antigen-specific CD4 and CD8 T cells have been detected in synovial fluid and synovial membranes. An important step in clarifying the pathogenesis of ReA would be to identify the target for the synovial T-cell response (176, 180). In the early phase of the disease, a CD4 T-cell response at the site of inflammation, triggered and maintained by the microbial components, is critical. Later, the CD8 T cells also become involved. It is possible that HLA-B27-restricted autoreactive cytotoxic T lymphocytes can maintain the inflammatory process even after the bacterial pathogen itself has been eradicated by antibacterial immune responses (3, 176). Fiorillo et al. have also shown that an autologous peptide derived from residues 400 to 408 (RRKWRRWHL) of the vasoactive intestinal peptide receptor 1 (VIP-IR) reacts with CD8T lymphocytes from ankylosis spondylitis (AS) patients in the context of arthritis-predisposing HLA-B27 as subtype but not with the arthritis-sparing B2709 subtype (52).

In ReA, the antibacterial Th1 cytokine response (production of IFN-γ, IL-2, and IL-12), which is necessary for the elimination of ReA-associated bacteria, is impaired. On the other hand, a Th2 response (IL-4 and IL-10) predominates and con-

tributes to bacterial persistence in the joints (30, 228). The pathogenesis of this Th1-Th2 imbalance is unclear, but it is likely that genetic factors of the host such as the polymorphism of cytokine genes (90) are causally involved (175). There is some evidence that TNF-α genotypes which seem to be associated with low TNF-α production are present at a higher percentage in ReA (180). Also, mice that are knockouts of the p55 receptor are more susceptible to infection by *Yersinia* and develop more severe arthritis (234).

Impaired peripheral-blood T-cell responses to ReA-triggering agents have been demonstrated. In patients with *Yersinia*-triggered ReA, there is a lower frequency of *Yersinia*-reactive T cells in peripheral blood than in patients with uncomplicated yersiniosis (214). When synovial T cells from ReA patients were stimulated in vitro with the triggering bacteria, the IFN-γ/IL-10 and the TNF-α/IL-10 ratios were clearly lower (228) compared with the response to *Borrelia burgdorferi* in Lyme arthritis patients. Because IFN-γ and TNF-α are crucial for the elimination of bacteria, the insufficient production of these cytokines in ReA patients contributes to bacterial persistence. Furthermore, ReA patients with lower TNF-α secretion have a longer disease duration than patients with higher secretion (30).

These findings may indicate a defective first-line defense in the patients developing arthritis that allows the bacterial antigens to reach the synovium, where they then initiate the specific T-cell responses (226). In addition, cytotoxic T lymphocytes infected with *Yersinia* seem to have a reduce lytic capacity against the infected target cells (2).

Miscellaneous

The systemic nature of ReA has been difficult to explain until very recently. Poole (152) has shown that proteoglycan present in blood vessels, especially the aorta, aortic valves, bone, and ocular tissues, in experimental animal models contains the GI domain (versican and aggrecan) that binds to hyaluronic acid. When tissue damage occurs (secondary to trauma, inflammation, or infection) and the underlying immunogenetic condition permits a loss of T-cell tolerance, enhanced release of these molecules occurs. This may provide the stimulus for proinflammatory aggrecan or link protein-specific recruitment of T lymphocytes and monocytes to the affected tissues, leading to tissue damage.

CLASSIFICATION CRITERIA

The diagnostic, classification, and inclusion criteria of patients with ReA are heterogeneous (82). Wilkens et al. in 1981 proposed the preliminary criteria for Reiter's syndrome (219). Considering that ReA is a member of the SpA group, two sets of criteria, the Amor criteria and the European Spondyloarthropathy Study Group criteria, could be used for ReA diagnosis (43). Although studied as classification criteria, they are useful and valid as diagnostic criteria (7). In 1996, a group of experts during the Third International Workshop on Reactive Arthritis proposed for research purposes a set of nonvalidated criteria (178). These criteria are as follows: typical peripheral arthritis (predominantly lower limb, asymmetric oligoarthritis) plus evidence of preceding infection (when there has been clear clinical diarrhea or urethritis in the preceding 4 weeks, laboratory confirmation is desirable but not essential; when there has been no clear clinical infection, laboratory confirmation of infection is essential); laboratory tests for preceding infection include positive stool cultures, detection of *C. trachomatis* in the first portion of the morning urine or in a urogenital swab, anti-*Yersinia* and anti-*Salmonella* antibodies to LPS or other specific antigens of immunoglobulin G (IgG) plus IgA or IgG plus IgM subtypes, IgG, IgM, and IgA antibodies to *C. trachomatis* (sensitivity and specificity regarded as low), and detection of chlamydial DNA in the joint by PCR. The experts at the Workshop also state that patients with other known causes of mono- or oligoarthritis, such as other defined SpAs, septic arthritis, Lyme disease, and streptococcal ReA, are exclusion criteria for ReA. The presence of HLA-B27, extra-articular features of Reiter's syndrome (conjunctivitis, iritis, skin lesions, noninfectious arthritis, and cardiac and neurologic features), or typical SpA features (inflammatory back pain, alternating buttock pain, enthesitis, and iritis) are not required for diagnosis.

Another proposal for the classification of patients entering clinical and experimental studies has recently been published by a Mexican group (149). The sensitivity, specificity, and positive predictive value of any single or combination of criteria require evaluation in a prospective study.

EPIDEMIOLOGY

The prevalence of ReA has been calculated as 0.1% (27, 107), with incidence rates of 4.6 to 13 per 100,000 for postvenereal ReA and 5 to 14 per 100,000 for postenteric ReA (85, 107). In a recent Swedish study, the total annual incidence of ReA was 28 in 100,000 (188). An underestimation of ReA cases is possible mainly because of two reasons. First, a clear differentiation among SpA subgroups, especially in their early stages, may not always be possible owing to overlapping clinical features (107, 160, 179). To exemplify this, in a community-wide epidemiologic study, Boyer et al. found that 36% of the ReA patients had not been correctly classified (24). Second, and very important for clinicians, is that as many as 36% of chlamydial and 26% of enteric ReA cases have asymptomatic triggering infections (107, 222).

While enteric ReA occurs most commonly following dysenteric outbreaks, sexually acquired ReA is the endemic form of ReA (81, 160). The causative infection is reported to be identified in 40 to 56% of patients with ReA. Genitourinary tract infection with *C. trachomatis* is the more commonly recognized cause of ReA in developed countries (in the United States it has been identified as the preceding infection in 42 to 69% of patients with urogenic ReA). Infections with enterobacteria are more common triggers in developing countries (98). *Yersinia* or *Salmonella* are the causative pathogen in 52% of patients with enteric ReA, with *Salmonella* being more common than *Yersinia* (33 and 18%, respectively). Although *Yersinia* is a relevant pathogen in continental Europe, it seems to be rather rare in the United Kingdom and United States (50).

Changes in the epidemiology of ReA have been reported. Recent data indicate a 30% decrease in prevalence of *Yersinia* arthritis in Finland, with no changes in the number of reported cases of *Salmonella*-triggered ReA. This decrease is probably

TABLE 2. Arthritogenic agents implicated in ReA[a]

Well-defined agents	Probable and potential agents	
Campylobacter jejuni	Amebae	HIV
Chlamydia trachomatis	B-19 parvovirus	*Lactobacillus* spp.
***Salmonella enterica* serovars *Typhimurium enteritidis*, Paratyphi B and C**, and **others**	*Bacillus cereus*	*Leptospira*
	Bartonella	*Mycoplasma hominis* and *M. fermentans*
Shigella flexneri*, *S. sonnei and ***S. dysenteriae***	*Borrelia burgdorferi*	*Neisseria gonorrhoeae*
Ureaplasma urealyticum	*Brucella abortus*	*Neisseria meningitidis* serogroup B
Yersinia enterocolitica* O3, O8, and O9** and ***Y. pseudotuberculosis	*Calmette-Guerin Bacillus*	*Propioibacterium acnes*
	Chlamydia pneumoniae	*Pseudmonas migulae, P. fluorescens,* and *P. putida*
	Clostridium difficile	
	Cryptosporidium	*Rickettsia ricketsii*
	Escherichia coli	*Staphylococcus aureus*
	Gardnerella vaginalis	*Staphyloccus aureus*
	Giardia lamblia	*Staphylococcus epidermis*
	Beta-hemolytic streptococci	*Streptococcus salivarius*
	Hafnia alvei	*Strongyloids*
	Helicobacter cinaedi	*Tropheryma whippelii*
	Helicobacter pylori	
	Hepatitis B vaccine	

[a] Data are from references 53, 71, 175, 200, and 201.
[b] Bold type indicates bacteria dependent on HLA-B27.

related to a decline in the rate of sexually transmitted disease secondary to the awareness of human immunodeficiency virus (HIV) infection. In contrast, in South Africa, where ReA used to be extremely rare and where HLA-B27 has a prevalence of less than 1%, the prevalence of ReA is now increasing in the wake of the HIV epidemic (98, 142, 223).

ETIOLOGIC AGENTS

With the increasing awareness of ReA, the list of causative agents is still growing, and it has become clear that different infectious agents can trigger the same clinical picture (53). Table 2 lists the ReA-triggering agents and their association with HLA-B27. Although efforts have been made to characterize the microorganisms linked to ReA, no definite common feature has so far emerged. *Yersinia*, *Salmonella*, *Shigella*, *Chlamydia*, and *Campylobacter* (pathogens causing HLA-B27-associated disease) all have a capacity to cause the primary infection in mucosal tissues, have LPS as a part of their outer membrane, exert intracellular parasitism, have a similar type of peripheral joint involvement, and contain virulence factors which help them to evade the host defense mechanisms and survive and disseminate in the body (61, 200, 226).

A prominent IgA humoral immune response is also seen with these pathogens. An important and still unanswered question is why only 1 to 10% of people infected with microorganisms known to trigger ReA actually develop the disease. Table 3 summarizes the incidence of ReA following infection by the main etiologic agents. It should be noted that the incidence of ReA strongly fluctuates according to various factors, e.g., the rate of enteric infections in a given area.

C. trachomatis, an obligate intracellular organism, is the most common sexually transmitted bacterial pathogen in the United States (145). Approximately 1% of men presenting with nongonococcal urethritis develop ReA (132). Evidence of urogenital *C. trachomatis* infection is found in 36 to 50% of the posturethritic cases of Reiter's syndrome and in 69% of the patients who have signs of urogenital inflammation at the time of examination (184).

C. jejuni is the leading cause of bacterial gastroenteritis in many Western countries. The incidence of ReA following *C. enterocolitis* is 2 to 3% (range, 0.6 to 24%) (46). The calculated incidence of ReA after *Shigella* infection is 1 in 10^3. In a localized outbreak with the same agent, the rate of arthritis was 1.2% (124, 185). The reported incidence of *Salmonella*-induced ReA is between 1.2 and 7.3%, and in outbreaks the frequency was as high as 19% (83, 125, 212). Concerning *Salmonella* serotypes, 60% of *Salmonella*-induced ReA cases are triggered by *S. enterica* serovar Typhimurium and 25% are triggered by *S. enterica* serovar Enteritidis (128, 147). The most common triggering agents in childhood bacterial reactive arthritis are *Y. enterocolitica* and *Y. pseudotuberculosis*; the incidence ranges from 5 to 35% (194).

CLINICAL ASPECTS

ReA affects people in the second to fourth decades of life and occurs 1 to 4 weeks following genitourinary (male-to-female ratio, 9:1) or enteric (male-to-female ratio, 1:1) infections (12, 95). ReA not only affects the joints but also is a systemic disease, and serious visceral involvement (cardiac, renal, or neural abnormalities) may develop. In the acute phase of ReA, no simple relationship exists between extra-articular features and the nature of the inciting infection, and

TABLE 3. Incidence of ReA after infection by the main etiologic agents

Etiologic agent	Incidence of ReA (%)	Reference(s)
Chlamydia trachomatis	1	132
Campylobacter jejuni	2–3	46, 124
Shigella flexneri	1.2	124, 185
Salmonella	1.2–14	123, 125, 128, 129, 171
Yersinia enterocolitica	5–33	194

TABLE 4. Clinical manifestations of ReA and their frequency[a]

Clinical manifestation	Symptom (frequency [%])
Peripheral arthritis syndrome	Large lower limb nondestructive acute asymmetric oligoarthritis
	Chronic-recurrent arthritis (15–30%)
	Sausage digits (16%)
Enthesopatic syndrome	Heel pain, Achilles tendonitis, pain at the tibial tubercle (30%)
Pelvic and axial syndrome	Inflammatory low back pain: sacroiliitis (14–49%), spondylitis (12–26%), inflammation of ligamentous or tendinous insertions in the ischial tuberosity (15–30%)
Extramusculoskeletal syndrome	Eye: conjunctivitis (35%), iritis (5%); keratitis, corneal ulceration, episcleritis, retrobulbar neuritis and hyphema
	Genitourinary: urethritis, prostatitis (80%), hemorrhagic cystitis, cervicitis
	Gastrointestinal: diarrhea, endoscopic "bowel lesions" (25–70%)
	Skin: keratoderma blennorrhagica (5–30%), circinate balanitis (20–4%), oral ulcers (5–10%), hyperkeratotic nails (6–12%), erythema nodosum
	Cardiovascular system: aortic disease, EKG conduction abnormalities (5–14%)
	Central nervous system peripheral/cranial nerve palsy, Parsonage Turner syndrome, motor deficits.
	Renal: proteinuria, microhematuria, aseptic pyuria, glomerulonephritis, IgA nephropathy

[a] Data from references 7, 12, 76, 98, 103, and 183.

the clinical characteristics of joint disease associated with *C. trachomatis* infection and those associated with postenteric arthritis are virtually identical.

ReA combines four syndromes: (i) an enthesopathic syndrome (135), (ii) a peripheral arthritis syndrome (an asymmetric acute or subacute oligoarthritis of the lower limbs), (iii) a pelvic and axial syndrome (spinal involvement with sacroiliitis), and (iv) an extramusculoskeletal syndrome. Table 4 summarizes the clinical manifestations of ReA, and Table 5 summarizes the sensitivity and specificity of some of them.

Articular Findings

The most frequent presentation is nondestructive acute oligoarthritis of large lower limb joints (an average of four joints are affected). The sensitivity of asymmetric oligoarthritis distribution is 44%, and the specificity is 95%. Very large knee effusions are not unusual. When these effusions develop rapidly, they frequently result in popliteal cysts that may rupture and cause a pseudophlebitis syndrome. In *Chlamydia*-associated arthritis, the knees are involved in 70% of cases, the ankles are involved in 57%, and the toes are involved in 35%; the wrists and fingers can be involved in as many as 45% of patients (84). The average duration of the arthritis is 4 to 5 months, but two-thirds of patients have mild musculoskeletal symptoms that persist for more than 1 year. Recurrent attacks are more common in patients with *Chlamydia*-induced ReA. Approximately 15 to 30% of patients develop chronic or recurrent arthritis, sacroiliitis, or spondylitis, and most of these patients have a positive family history for SpA or are positive for HLA-B27 (98).

Diffuse swelling of an entire finger or toe ("sausage digit") occurs in 16% of patients and has a sensitivity of 27% but a high specificity of 99% (103). Enthesitis (inflammation of the ligaments and tendons at the sites of their insertion into the bone) in the European Spondylarthropathy Study Group study was found in approximately 30% of ReA patients and in approximately 20% of control patients with no SpA. Secondary to enthesitis, patients may have heel pain (sensitivity of 52% and specificity of 92%), Achilles tendonitis, or pain at the insertion of the patella tendon into the tibial tubercle.

Inflammatory low back pain (sensitivity of 71% and specificity of 77%) secondary to sacroiliitis or spondylitis or due to inflammation of ligamentous or tendinous insertions in the ischial tuberosity is another distinctive feature (183). Affection of the cervical spine is unusual but may occur and may even result in atlantoaxial subluxation (54).

Extra-Articular Findings

Conjunctivitis occurs in one-third of patients with ReA and in the majority of patients with *Shigella*, *Salmonella*, and *Campylobacter* infections. Its incidence is only 10% in patients with *Yersinia* arthritis and in about 35% of patients with postvenereal ReA. It usually appears at the same time as flares of arthritis and has a strong tendency to recur. It is frequently mild, transient (subsides in 1 to 4 weeks), and easily missed. It is unilateral or bilateral and frequently is associated with a sterile discharge. Acute anterior uveitis (iritis) may occur at some time in about 5% of patients. Keratitis, corneal ulceration, episcleritis, retrobulbar neuritis, or anterior chamber hemorrhage (hyphema) may be present in persistent or chronic disease (76, 95, 103).

Urethritis may be a principal feature of ReA even in some postdysenteric cases. As a precipitating event, it precedes the symptoms of ReA by 1 to 3 weeks. Between 70 and 80% of women and a substantial proportion of men infected with *C. trachomatis* have no genitourinary symptoms (160). Nonspecific urethritis is mild, painless, and associated with nonpurulent clear mucoid urethral discharge. Prostatitis is common and has been found up to 80% of patients. Hemorrhagic cystitis may develop (97). In female patients, nonspecific or mu-

TABLE 5. Sensitivity and specificity of "distinctive" clinical features in ReA[a]

Clinical feature	Sensitivity (%)	Specificity (%)
Asymmetric oligoarthritis	44.3	95
Sausage digit	26.6	99
Heel pain	51.6	92.2
Inflammatory dorsal or lower back or buttock pain	71.4	77.3

[a] Data are from reference 7.

copurulent cervicitis with or without easily induced cervical bleeding and/or abdominal pain may occur (12, 144).

Gastrointestinal symptoms are absent or mild in ReA triggered by *Yersinia*, but more severe and of longer duration in patients with *Salmonella*- and *Campylobacter*-induced ReA (50, 124). The interval from *Salmonella* infection to arthritis is <3 weeks in most patients. In cases of postdysenteric ReA, the longer the duration of diarrhea, the greater the likelihood of developing ReA (83, 125, 183). This phenomenon may reflect an abnormality at the level of the gut mucosal defense, allowing for enhanced colonization or delayed clearance of the pathogen. When ileocolonoscopy is carried out in patients with established ReA, either macroscopically or microscopically detectable lesions resembling ulcerative colitis or Crohn's disease are seen in almost 70% of cases. Gut inflammation is mainly subclinical, but there is a close correlation between disease activity in the joints and activity in the gut (140, 200). Even patients with sexually acquired ReA have colonoscopic lesions in about 25% of cases, suggesting that in some cases these lesions represent yet another extra-articular manifestation of SpA (100).

Mucocutaneous lesions are very specific (9). Keratoderma blennorrhagica or pustulosis palmoplantaris (5 to 30%) begins on the palms and soles as pustules; they gradually become covered with thick, horny crusts, and neighboring lesions may become confluent. Clinically and microscopically, these cutaneous lesions are difficult to differentiate from pustular psoriasis. Circinate balanitis (20 to 40%) is a well-defined, painless erythematous lesion with small, shallow ulcers of the glans penis and urethral meatus. Oral ulcers (5 to 10%), located in the hard and soft palate, gingiva, tongue, and cheeks, are characteristically painless, erythematous, and superficial. Hyperkeratotic nail (6 to 12%) and skin lesions, not easily distinguishable from pustular psoriasis, could also be present. Erythema nodosum is a well-recognized feature of *Yersinia* infection that typically occurs in women, especially those who are HLA-B27 negative, and the lack of gastrointestinal symptoms in these cases is also documented. *Yersinia* infections can account for up to 15% of patients in erythema nodosum series, and these cases may even mimic sarcoidosis (57).

Cardiac manifestations include aortic disease and conduction delays. The aortic ring and ascending aorta are the usual sites of involvement, and aortic incompetence (dilatation-regurgitation) is usually a late finding and is often asymptomatic. ReA aortic disease may be difficult to distinguish from that of syphilis, since pathologically there is virtually no difference (74). Electrocardiographic abnormalities are recorded in 5 to 14% of patients. The most commonly reported conduction abnormality in patients with long-standing disease (more than 10 years) is first-degree atrioventricular (AV) block, which could progress to second-degree AV block (Wenckebach type) and complete heart block (41).

Proteinuria, microhematuria, or aseptic pyuria is seen in about 50% of patients with sexually acquired ReA and is usually asymptomatic. Glomerulonephritis and IgA nephropathy are rare. Severe systemic necrotizing vasculitis (21), thrombophlebitis, purpura, livedo reticularis, and amyloidosis (44) have been reported as rare complications in chronic disease (222). Transient neurologic dysfunction, such as peripheral or cranial nerve palsy, Parsonage-Turner syndrome, and hemiplegia have also been described.

LABORATORY FINDINGS

Laboratory abnormalities are nonspecific and include mild normocytic anemia, moderate neutrophilic leukocytosis, and elevated erythrocyte sedimentation rate, C-reactive protein level, and serum complement levels. Urinalysis should be carried out at presentation and should be repeated during follow-up to detect possible aseptic pyuria due to urethritis. Antinuclear antibody and rheumatoid factor are negative. Antineutrophil cytoplasmic antibodies against lactoferrin and myeloperoxidase were found in one study in 12 of 22 patients with ReA, but this is not supported by others (126, 192).

Joint fluid should always be aspirated when possible. Synovial fluid may be mildly to severely inflammatory and may contain large macrophages with vacuoles that contain nuclear debris and whole leukocytes which are called Reiter's cells and are not specific for ReA. Synovial tissue and synovial fluid cultures are negative. Crystals are not present. Synovial biopsy is not of diagnostic value since the inflammation is nonspecific (inflammatory changes, including vascular congestion and perivascular polymorphonuclear cell infiltration) but may be valuable in the exclusion of alternative diagnoses.

RADIOGRAPHIC FINDINGS

Although radiographic findings are not essential for diagnosis, they are important in the evaluation of patients with ReA. Early in the disease, radiographs may be entirely normal. Acute attacks of arthritis may be accompanied by soft tissue swelling. With repeated episodes of arthritis, permanent radiographic abnormalities may appear in up to 20% of patients (97).

The most characteristic sites of involvement are the small joints of the foot, calcaneus, ankle, and knee. In the axial skeleton, the sacroiliac joints, spine, symphysis pubis, and manubriosternal joints are frequent target areas. Enthesopathic lesions can be visualized at an early stage by focal uptake of 99 mTc-methylene diphosphonate and by magnetic resonance imaging.

Asymmetric reactive bone proliferation at the sites of inflammation is a helpful radiographic feature for diagnosis. Later fluffy periosteal reaction and erosions may be seen at the sites of ligamentous and tendon insertions, especially the Achilles tendon, the plantar tendons, and the fascia. Although magnetic resonance imaging has been used for diagnosing enthesitis, ultrasonography is the preferred technique, being both noninvasive and sensitive (148). Ultrasonography is also useful in demonstrating plantar fasciitis.

Erosive joint damage especially affects the small joints of the feet, with 12% of patients exhibiting foot deformities (144). Subchondral sclerosis, eburnation, and adjacent periostitis, as well as intra-articular bony ankylosis in the small joints, have also been observed.

Asymmetric sacroiliitis can be demonstrated radiologically in over one-third of patients with chronic ReA (133, 157, 163). In the early stages of sacroiliitis when radiographs may be negative, computed tomography may be useful for demonstrating early erosions and sclerosis. Magnetic resonance imaging is

TABLE 6. Criteria used for the identification of the triggering bacterium as a probable or possible cause of ReA[a]

Bacterium	Criterion
Chlamydia	1. Probable ReA
	Chlamydia positive in urogenital smear plus symptomatic urethritis
	IgG ≥ 1/64 plus positive IgA or IgM plus *Chlamydia* positive in urogenital smear or symptomatic urethritis
	Antibody titers of 2 standard deviations (SD) above normal for IgG plus IgA or IgM plus symptomatic enteritis or Widal agglutination ≥ 1/320 (normal <1/60)
	2. Possible ReA
	Chlamydia positive in urogenital smear or IgG ≥ 1/64 plus positive IgA or IgM
Yersinia	1. Probable ReA
	Yersinia-positive stool culture
	Antibody titers of 3 SD above normal for IgG plus IgA or IgM
	Antibody titers of 2 SD above normal for IgG plus IgA or IgM plus symptomatic enteritis
	2. Possible ReA
	Antibody titers of 2 SD above normal for IgG plus IgA or IgM or Widal agglutination > 1/320 (normal, <1/160)
Salmonella	1. Probable ReA
	Salmonella-positive stool culture
	Antibody titers of 3 SD above normal for IgG plus IgA or IgM
	Antibody titers of 2 SD above normal for IgG plus IgA or IgM plus symptomatic enteritis
	2. Possible ReA
	Antibody titers of 2 SD above normal for IgG plus IgA or IgM
Campylobacter	1. Probable ReA
	Campylobacter-positive stool culture
	Antibody titers of 3 SD above normal for IgG plus IgA or IgM
	2. Possible ReA
	Antibody titers of 2 SD above normal for IgG plus IgA or IgM

[a] Always in the presence of an arthritis either asymmetrically or predominantly of the legs. For probable ReA, only one of the criteria has to be fulfilled. Data are from references 50, 71, 107, and 113.

more sensitive than computed tomography in assessing cartilage changes, however. In the spine, asymmetric paravertebral ossification involving the lower three thoracic and upper three lumbar vertebrae is characteristic.

DIAGNOSIS

The diagnosis of ReA is still a problem because the preceding bacterial infection is often asymptomatic, identification of the etiologic agent is difficult at the time when the arthritis occurs, and no validated criteria for the diagnosis of ReA are currently available (149, 179). Criteria from the American College of Rheumatology (ACR) require that the diagnosis of ReA be based on a documented urogenital *C. trachomatis* infection or a gastrointestinal infection by a relevant enteric pathogen. Patients meeting all ACR criteria except that specifying a previous infection usually are classified as having undifferentiated oligo- or monoarthritis (84). On the other hand, as screening methods for identification of *Chlamydia* have improved, patients who have chlamydial antigens or nucleic acids in the joint but who do not meet ACR criteria for ReA are being recognized. Some authors designate these patients as simply having *Chlamydia*-associated arthritis (84, 221).

There is no single category of laboratory tests that can be used to diagnose ReA and to determine the responsible organism (28). Currently, the best diagnostic results come from combining laboratory and clinical information (56). The diagnostic criteria for ReA shown in Table 6 were used in a recent study by Fendler et al. (50) and resemble those used in other studies (71, 107, 113). It has been reported that elevated C-reactive protein levels, genitourinary symptoms, metatarsophalangeal joint involvement, and HLA-B27 could predict the diagnosis of ReA with a sensitivity of 69.2% and a specificity of 93.5% (106).

Evidence of urogenital *C. trachomatis* infection is found in 36 to 50% of the posturethritic cases of ReA and in 69% of the patients who have signs of urogenital inflammation at the time of examination (184). The diagnosis of *Chlamydia*-induced arthritis is based on the presence of a preceding symptomatic urethritis/cervicitis (154), positive *Chlamydia*-specific antibodies (the microimmunofluorescence test is still considered the "gold standard" as a serological test for *Chlamydia*-specific antibodies), and/or the detection of *C. trachomatis* in the urogenital tract. Because there is a poor overlap between these three variables, all three should be used for diagnosis (50).

The microimmunofluorescence test has been criticized for its requirement for considerable expertise, its subjective interpretation, and its unsuitability for testing large numbers of specimens (15). *Chlamydia* culture has been considered the gold standard for diagnosis (198); however, its sensitivity has been estimated at only 70 to 80% or less for women with cervical infection. This has led to the suspicion of "inapparent-nonculturable" chlamydial infections in humans and the need for better diagnostic tools.

The search for *Chlamydia* in the first portion of the morning urine by PCR or by ligase chain reaction seems to be an acceptable and relatively easy diagnostic approach with a result comparable to that demonstrated by urogenital swab (154). Antigen-detection tests (direct fluorescent-antibody assay, enzyme immunoassay [EIA], and immunoblotting), and nonamplified nucleic acid hybridization, as well as newer technologies based on amplified DNA assays (PCR, ligase chain reaction, strand displacement assay, hybrid capture system, and transcription-mediated amplification of RNA) may provide improved sensitivity, lower expense, availability, or timeliness of results over culture (15, 145). The sensitivities and specificities of nucleic acid amplification tests are all high, ranging from 82 to 100%. The sensitivity of antigen detection tests (EIA and

TABLE 7. Sensitivity, specificity, positive predictive value, and negative predictive value obtained for the different anti-*Chlamydia* antibody assays and their combinations[a]

Isotype(s) considered	Sensitivity (%)	Specificity (%)	+PV[b] (%)	−PV[b] (%)
Serum antibodies				
IgG anti-MOMP	79	58	65	73
IgA anti-MOMP	53	63	59	57
IgG anti-LPS	89	42	61	80
IgA anti-LPS	68	58	62	65
IgG and/or IgA anti-MOMP or anti-LPS	100	21	56	100
Synovial fluid antibodies				
IgG anti-MOMP	77	80	83	73
IgA anti-MOMP	46	90	86	56
IgG anti-LPS	85	70	79	78
IgA anti-LPS	62	50	62	50
IgG and/or IgA anti-MOMP or anti-LPS	100	40	68	100

[a] Data are from reference 17.
[b] +PV and −PV, positive and negative predictive values, respectively.

direct fluorescent-antibody test) is slightly lower (70 to 80%), but the specificity remains high (96 to 100%) (144).

Differentiation between the *Chlamydia* species is crucial for diagnosis because of a high degree of cross-reactivity and a high prevalence of anti-*C. pneumoniae* antibodies. A substantial proportion of patients with *Chlamydia*-induced ReA can be antibody negative, resulting in low sensitivity. A peptide-based EIA detecting IgA and IgG antibodies against *C. trachomatis* in serum samples from patients with *Chlamydia*-triggered ReA has a sensitivity of 74% and a specificity of 84% (146). Antibodies of the IgG subclass alone do not sufficiently reflect a recent infection, because their levels can be elevated for months after an infection; therefore, determination of IgG antibodies should be combined with tests for IgM or IgA antibodies, with the last two indicating an acute or persistent infection.

As antigens, whole *C. trachomatis* or *Chlamydia* specific MOMP and/or LPS (13, 17) have been used. The specificity and sensitivity of currently available tests is not higher than 78 and 73%, respectively (182). Enzyme-linked immunosorbent assays (ELISAs) using synthetic peptides derived from species-specific epitopes in the variable domain IV of the MOMP of *C. trachomatis* and not homologous to *C. pneumoniae* have been developed (16). The determination of synovial fluid IgG anti-MOMP antibody could be particularly useful since a sensitivity and specificity of roughly 80% are observed (17). The specificity reaches 90% with the determination of synovial fluid IgA anti-MOMP antibody. A major disadvantage of these tests is that they are only qualitative (17). Another ELISA is based on an exclusively *Chlamydia*-specific recombinant fragment of the total LPS. This genus-specific antigen allows the detection of antibodies against *C. trachomatis*, *C. pneumoniae*, and *C. psittaci* (17). The reported sensitivity, specificity, and predictive values of these tests are showed in Table 7.

For the diagnosis of enteric ReA, a search for the triggering bacterium in stool cultures seems to be useful only for patients with preceding symptomatic enteritis. *Yersinia* or *Salmonella* is detected in the stool in 9% of patients who had diarrhea in the preceding 4 weeks (50). In *Yersinia* ReA, at the time the articular symptoms manifest themselves, stool cultures are rarely positive; because the organism requires special culture techniques, the diagnosis is often missed by stool cultures (194). The positive predictive value for *Yersinia* and *Salmonella* serologic tests for the diagnosis of ReA is not certain at present because there is no gold standard. Much less information is available about the value of serologic testing in the diagnosis of *C. jejuni*- or *Shigella*-induced ReA, which has not been established (100). *Campylobacter* may be identified as *C. jejuni* or *C. coli* by conventional phenotypic tests and serotyping by passive hemagglutination.

Salmonella and *Yersinia* antibodies can be studied by the agglutination test (Widal) and ELISA. The Widal agglutination test detects IgM antibodies and can therefore be used as evidence of recent bacterial infection, but, especially for *Salmonella*, its sensitivity is relatively low (64%), even in acute infections (178). Agglutination when only IgA antibodies are present may give false-negative results. ELISA distinguishing between antibodies to different immunoglobulin classes appears preferable to the agglutination technique. Combining IgG and IgA or IgM, a specificity of 90% can be assumed for *Yersinia*- and *Salmonella*-specific serologic tests.

For *Yersinia* infections, most data have been obtained by using an EIA with a sodium dodecyl sulfate extract of LPS from *Yersinia* or by using an immunoblot analysis with *Yersinia* OMP as the antigen (182). In acute *Yersinia*-induced ReA, IgG plus IgA antibodies can be detected in close to 100% of patients. A persistence of IgA antibodies in the sera of patients with *Yersinia* arthritis for 14 to 16 months after onset of the infection is found in 84% of the patients (67), and peak levels of IgA correlate directly with the severity of arthritis (56, 67). In patients without arthritic symptoms, these antibodies disappear in 5 months. IgG antibodies to *Yersinia* also persist longer in arthritic patients than in patients without arthritis, but not as consistently as IgA antibodies. IgM antibodies persist for only 1 to 3 months after the onset of infection (67). It is recommended to test for IgG, IgM, and IgA isotypes in patients with acute ReA and for IgG and IgA isotypes in patients with chronic ReA (56, 84).

ELISA is by far the most sensitive method to detect anti-*Salmonella* antibodies acute and late infections), it has a sensitivity of approximately 92% (125). These antibodies levels tend to persist longer among patients with ReA (9 to 14 months) than in those with uncomplicated enterocolitis (4 months) (129). In salmonellosis, a response in all immunoglobulin classes is seen, in contrast to *Yersinia*-triggered ReA, where IgA antibodies and particularly those of the secretory IgA class and the IgA2 subclass persist (125). No good serologic test is available for the diagnosis of *Shigella* infections (50).

Finally, because simultaneous multiple sexually-transmitted infections are common, serologic tests for HIV, syphilis, and gonococcal cultures should be done in patients with sexually transmitted ReA (144).

PCR Amplification

Synovial membrane biopsy specimens are more suitable for PCR than are synovial fluid specimens for detection of bacterial DNA (26). However, these amplification methods have not been standardized (222). Using a nested PCR approach simultaneously targeting DNA sequences of multiple bacterial spe-

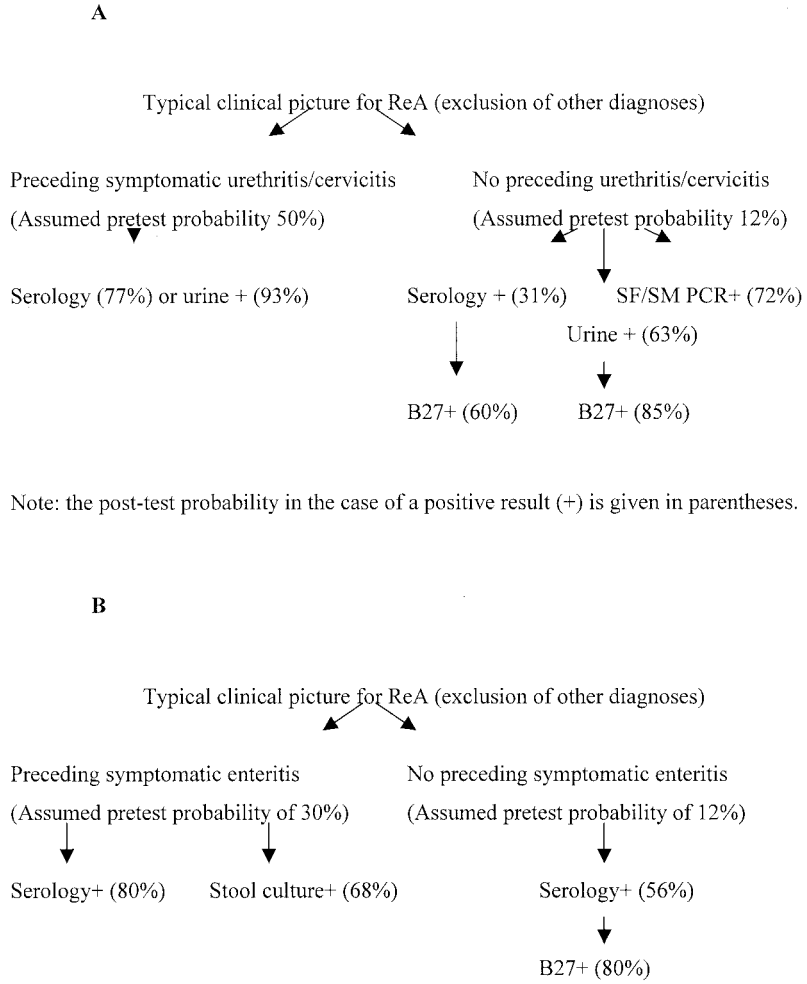

FIG. 2. (A) Diagnostic approach to *Chlamydia*-induced ReA. (B) Diagnostic approach to *Yersinia*- or *Salmonella*-induced ReA. Reprinted from reference 182 with permission.

cies in synovial fluid from arthritis patients, Braun et al. detected DNA from *B. burgdoferi*, *C. trachomatis*, *C. pneumoniae*, *Campylobacter jejuni*, or *Shigella flexneri* in 16 of 104 samples of patients with uSpA (29, 30).

Chlamydial DNA and mRNA has been found in synovial membrane biopsy specimens, and *C. trachomatis* is found by PCR in peripheral blood cells but not in serum of patients with early *Chlamydia*-induced ReA (96, 179). Positivity for *Chlamydia* is found by PCR in 65% of patients with Reiter's syndrome and 42% of patients with other types of ReA. In patients with undifferentiated arthritis but with a joint pattern compatible with ReA, chlamydial DNA has been detected by PCR in approximately 30% of cases. Chlamydial DNA was also found in control groups such as patients with RA (21%), patients with OA (35%), and healthy subjects (172, 220). The above results, along with data showing the lack of correlation between the presence of chlamydial DNA in the joint and a specific cellular or humoral immune response to the organism (220), limit the usefulness of PCR as a diagnostic test (38, 86). There is no agreement at the moment about the optimum technique to detect *Chlamydia* by PCR (182). *Salmonella*- or *Yersinia*-specific PCR for joint material does not currently play a role in the diagnosis of ReA.

HLA-B27

Routine HLA-B27 testing is not clinically helpful, because SpAs can occur in the absence of the allele. HLA-B27 is present in 8% of healthy Caucasians, of whom about 90% will never develop SpA. In recent studies based on epidemics and/or on community investigations, association with HLA-B27 is not higher than 50% in *Salmonella*-, *Campylobacter*-, and *Chlamydia*-induced ReA (182). The frequency of B27 in *Shigella*-induced ReA is approximately 80% (180). HLA-B27 positivity is more likely in patients with chronic or relapsing arthritis, uveitis, aortitis, sacroiliitis, and spondylitis (36). As a summary of this section, Fig. 2 shows the diagnostic approach proposed by Sieper et al. (182).

DIFFERENTIAL DIAGNOSIS

In patients presenting with a clinical picture suggestive of ReA, a variety of other conditions should also be considered (157, 183). Table 8 lists the other conditions in the differential diagnosis.

Disseminated gonococcal infection is more often characterized by acute onset with migratory polyarthralgia and tenosyn-

TABLE 8. Differential diagnosis of ReA

Inside the SpA group	Other "boundaries" of ReA	Outside the SpA group
Psoriatic-associated arthropathies	Rheumatic fever	Other sexually acquired arthritis (gonococcal, HIV)
SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, osteitis)	Parasitic arthritis	RA
Crohn's disease/ulcerative colitis-associated arthritis	*Brucella* ReA	Gouty arthritis
AS		Behcet syndrome
		Parvovirus arthropathies
		Lyme disease
		Sarcoid arthritis
		Occult celiac disease
		Pseudoinflammatory lower back pain

ovitis in the small joints of the hands. A helpful diagnostic clue to gonococcal arthritis is the presence of a pustule with an erythematous base on the hand or foot. If a gonococcal infection is suspected clinically, a therapeutic test using antibiotics exclusively is justified because the arthritis subsides dramatically within 3 days and completely within 10 days.

AS has a similar axial skeletal distribution to ReA, but significant peripheral articular involvement is less frequent. In AS, symmetric sacroiliac joint changes and symmetric slender bony outgrowths of the spine, vertebral body osteitis, apophyseal joint ankylosis, and intra-articular osseous fusion of the sacroiliac joint are more common.

Psoriatic arthritis shares certain findings with ReA such as the asymmetric pattern of arthritis, sausage digits, distal interphalangeal joint involvement, and the histology of skin lesions. Nevertheless, in psoriatic arthritis the involvement of the upper extremities and distal interphalangeal joint abnormalities in both upper and lower extremities are more common.

RA is a symmetric and erosive disease without severe sacroiliac and thoracolumbar spinal changes. Gouty arthritis often affects older men and presents with podagra or acute arthritis resolving within days. In Behcet's syndrome, painful oral or genital ulcerations and total or posterior uveitis help to make the diagnosis. Sarcoid arthritis usually presents with bilateral ankle joint involvement and bilateral lymphadenopathy. In patients with ReA and high fever, Still's disease or rheumatic fever should be considered in the differential diagnosis. Other conditions that can be considered in the differential diagnosis are undifferentiated persistent arthritis, occult celiac disease, inflammatory bowel disease-associated inflammatory joint disease, parvovirus arthropathies, Lyme arthritis, and pseudoinflammatory lower back pain (late sequelae of dorsolumbar Scheuermann's disease) (7, 107).

COURSE

The course of ReA can follow various patterns: short and self-limiting, recurrent, or continuous and unremitting. The duration of acute ReA varies among reports. The differentiation between acute and chronic ReA has been set by consensus at 6 months (28). In Finnish studies, the average duration of arthritis was 3 to 5 months. Enthesopathy, balanitis, and psoriatic lesions tend to persist even after the joint inflammation has disappeared and laboratory markers of inflammation have returned to normal. When all symptoms are taken into account, 75% of patients are in complete remission at the end of the second year after onset. In the Finnish study, 15% of patients developed chronic sequelae or proceeded into chronic SpA (89, 120). Leirisalo-Repo et al. reported that only 20% of their cases of inpatient *Salmonella* arthritis were completely normal at a mean of 11 years (119). A prolonged (>1-year) extension of acute arthritis has been described in about 4% of cases of *Yersinia* arthritis, in 19% of cases of *Salmonella* arthritis, in 19% of cases of *Shigella* arthritis, and in 17% of cases *Chlamydia* arthritis (91, 119, 120). Depending on the triggering infection and on the follow-up time, chronic arthritis is observed in 2 to 18% of patients, sacroiliitis is observed in 14 to 49%, and AS is observed in 12 to 26% (91, 117, 200). In one of the earliest studies of ReA, chronic disability was found in 40 of 100 persons who were available for reexamination 25 years after onset of disease (34).

PROGNOSTIC FACTORS

The 20-year prognosis in ReA is influenced by four major factors: the nature of the triggering infection, the presence of HLA-B27, the patient's gender, and the presence of recurrent arthritis (100). Persistent or recurrent urogenital infection or a chronic inflammatory focus in the gut may contribute to the progression of acute ReA to chronic SpA (117). Table 9 illustrates the importance of the organism that triggers the infection in the long-term prognosis of patients with ReA.

The presence of HLA-B27 in ReA has been linked to more severe disease, higher frequencies of sacroiliitis and extraarticular manifestations, and an increased likelihood of persistent arthropathy (according to some investigators but not others) (160). Male gender, positive family history for SpA or AS, and the presence of coxitis are adverse prognostic factors. Such

TABLE 9. Long-term (10- to 20-year) prognosis of ReA[a]

End point	% of patients with end point after infection with:			
	Yersinia	*Salmonella*	*Shigella*	*C. trachomatis*
Recovered	45	40	20	30
Arthralgia	20	20	NA[b]	68
Recurrent arthritis	6	22	18	38
Chronic arthritis	4	19	19	17
AS	15	12	14	26
Radiologic sacroiliitis	20	14	32	49

[a] Data from references 84, 95, 117, 118, 120, and 171. The percentage of patients achieving different end points in ReA induced by genitourinary and enteric bacteria is shown.
[b] NA, data not available.

TABLE 10. Therapeutic management of ReA

Therapy
Nonpharmacologic
Patient education
Management of extraarticular manifestations: use of topical corticosteroids, mydriatic agents, cycloplegics
Physical therapy
Occupational therapy
Pharmacologic
Acute presentation
NSAIDs: COX-1 and COX-2 inhibitors
Antibiotics: tetracycline, erythromycin, ciprofloxacin
Chronic or refractory presentation
Second-line or DMARDs: sulfasalazine, methotrexate, cyclosporine, gold salts, leflunomide, 6-mercaptopurine, levamisole, bromocriptine
Biological agents: infliximab, etanercept, adalimumab, thalidomide

patients have higher frequency of radiologic sacroiliitis, bamboo spine, and erosive coxitis.

Seven predictive factors are useful for assessment during the first 2 years of disease: hip arthritis, an erythrocyte sedimentation rate of >30 mm/h, poor efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs), limitation of range of motion of lumbar axis, sausage-like finger or toe, oligoarthritis, and onset before 16 years of age. If the hip is involved or if three factors are present, a poorer outcome is predicted (8, 97, 117).

THERAPY

Due to the poorly understood nature of its pathogenesis, there is no specific or curative treatment for ReA. As with any other articular inflammatory process, therapeutic management should be aimed at control or relief of pain, prevention of joint destruction and/or disability, preservation of joint function, and/or correction of joint deformities. This can be accomplished by nonpharmacologic and pharmacologic measures (Table 10).

Nonpharmacologic Approach

It is very important that patients should have adequate information about their illness, which will lead to a better disposition to confront it and also compliance with prescribed therapeutic regimens. Physicians should inform patients about their prognosis and potential late sequelae of their disease. The recurrent or relapsing nature of their complaints and the role of urogenital or enteric infections should be stressed, as well as proper means of avoiding them (202). Early rehabilitation measures are particularly indicated in patients with chronic disease and in the presence of severe joint stiffness or contractures and muscle atrophy.

Extra-articular manifestations should be monitored under the direction of the relevant specialist. It is important to emphasize that eye lesions should be managed with ophthalmologic advice. Even though conjunctivitis typically subsides without sequelae, slit lamp assessment is essential to diagnose uveitis, which, if untreated, may result in irreversible visual loss. Therapy for uveitis consists of topical corticosteroids, mydriatics, and cycloplegics (144). In patients with ReA and acute anterior uveitis, long-term treatment (12 months) with ciprofloxacin made no significant difference to the severity or natural history of disease (215).

Topical corticosteroids and keratolytic agents are useful for keratoderma blennorrhagica. Circinate balanitis should be treated with weak topical steroids such as hydrocortisone valerate cream. More resistant skin lesions usually respond to methotrexate or retinoids such as etretinate. Oral lesions resolve spontaneously and require no treatment.

Pharmacologic Approach

Acute presentation. Most patients with ReA have a good clinical response to NSAIDs (118, 170, 201). Pain at night and morning stiffness, particularly lower back pain and enthesopathic pain, in ReA are very sensitive to NSAIDs. However, data about the long-term efficacy of these drugs remain scarce. These agents, both COX-1 and COX-2 inhibitors, constitute a cornerstone in the pharmacological therapy of ReA. NSAIDs should be used early, at full doses, and regularly over several weeks or months to allow the patient to become more active and functional. It should be kept in mind that at times it may take a few weeks for the maximal effect to be achieved. No individual NSAID is definitely superior, although aspirin is not as effective as other NSAIDs, and the individual response to them varies from patient to patient (203). It has been suggested that even though NSAIDs do not directly affect metalloproteinase functions, they may potentiate the anti-collagenolytic/antiproteolytic potential of antibiotics, especially tetracyclines, by reducing edema and thereby facilitating the entry of the antibiotics to the sites of inflammation (114).

Steroids have only limited value for axial symptoms but are effective for peripheral arthritis. Intra-articular steroid injections, although less effective than in RA, benefit patients with mono- or oligoarticular disease. The systemic use of steroids is not indicated, except for short courses (no more than 2 to 4 months) if severe polyarthritis or progressive atrioventricular conduction disturbances are present (170).

Antibiotic use. The use of antibiotics in ReA remains controversial. Its use however, seems logical since the association of infection with ReA is well established. Eradication of the pathogen might help to ameliorate or prevent arthritis (119). A number of issues await further answers, however. First of all, it is not known if antibiotic treatment for the primary infection can prevent subsequent flare-up of ReA; second, it is not known if the use of antibiotics in established disease can shorten its course (100). Another issue that needs to be considered is that most bacteria responsible for ReA are intracellular and their eradication would therefore probably require a prolonged course of antibiotics. It is conceivable that early eradication of infection may diminish the antigen load and/or limit the dissemination of the infection and thereby modulate the severity of clinical expression (119).

The evidence gathered regarding antibiotic use suggests that in sexually acquired ReA, the use of appropriate antibiotics to treat the initiating urethritis can substantially decrease the risk of subsequent ReA in both the patient and the partner (118). In enteric ReA, however, regardless of the causative organism(s), antibiotic treatment is generally ineffective and its use after the onset of ReA is not recommended. A summary of the

TABLE 11. Evidence of the role of short-term antibacterial treatment in ReA

Reference	Study design	No. of patients and diagnosis	Intervention	Results
55	Open, randomized, prospective	40 entero-ReA (*Yersinia*, *Salmonella*, *Campylobacter*)	No treatment versus antibacterial agents (pivampicilin, pivmecillinam, doxycycline, erythromycin, co-trimoxazole, cinxacin)	No difference in duration of arthritis, grade of inflammation, number of joints involved, laboratory tests
123	Open	108 enterocolitis	65 treated with antibacterials (9 days) (ciprofloxacin, norfloxacin, doxycycline, co-trimoxazole, pivmecillinam-pivampicillin)	No effects of antibiotics on prevention of development of arthritis
11	Retrospective	224 episodes of genitourinary tract infections (60 ReA patients with urogenital infections)	59 episodes, no treatment; 97 episodes, penicillin treatment; 68 episodes, erythromycin or tetracyclin therapy for at least 1 day	37% of those not treated or treated with penicillin developed ReA, compared with 10% of those treated with erythromycin or tetracycline

trials that study the benefit of long- and short-term antibiotic treatment for ReA is shown in Tables 11 and 12.

(i) Antibiotic trials in urogenital arthritis. Proper and prompt treatment of new genitourinary tract infections dramatically reduces relapses of ReA. This was clearly shown in a study performed in the Greenland population, which has a high frequency of HLA-B27 antigen and ReA, in which the incidence of postvenereal ReA relapses was significantly reduced from 37% in untreated or penicillin (ineffective for *Chlamydia*)-treated patients to 10% following short-term (10 days) treatment with erythromycin or tetracycline (11).

A 3-month placebo-controlled prospective study with lymecycline (a tetracycline with good absorbance in the gastrointestinal tract) in 21 patients with acute chlamydial ReA showed a beneficial effect on the duration of the arthritis in the treated group (50% of patients recovered at 15 weeks) compared to placebo (50% of patients recovered at 39.5 weeks). Also, the elevated erythrocyte sedimentation rate and C-reactive protein levels normalized more rapidly in the lymecycline group. Side effects were mild and uncommon and occurred with similar frequency in both groups (113). Recently, this group of patients was reevaluated 10 years after the initial report in order to assess the natural history of ReA following a 3-month course of lymecycline. The results showed that long-term lymecycline treatment did not change the natural history of the disease (108). It was subsequently suggested that the initial benefit of lymecycline may at least partially be due to other, nonbactericidal effects of this antibiotic, such as suppression of neutrophil function and anticollagenolytic potential (115). Improvement in clinical parameters after a 3-month course of minocycline in 10 patients with *Chlamydia*-induced ReA has also been reported (150).

In contrast, controlled studies with prolonged use of antibiotics in chronic ReA did not show benefit (187, 221). Sieper et al. (181) did show, however, that in the subgroup of 13 patients with *Chlamydia*-induced ReA, ciprofloxacin was superior to placebo in nearly all variables evaluated; however, due to the small number of patients, none of the differences reached significance.

It is recommended that the use of antibiotic therapy be mandatory in *C. trachomatis* infection irrespective of the presence of arthritis. The patient's sexual partner(s) should be treated simultaneously (144). For urethritis due to *C. trachomatis*, either doxycycline (100 mg twice a day) or ofloxacin (300 mg twice a day) for 7 days or azithromycin (1 g orally as a single dose) should be used. In patients with acute *Chlamydia*-induced ReA, a prolonged course of antibiotics (4 to 12 weeks), either tetracycline or ciprofloxacin, should be given (171). Antibiotics do not appear to be of value in patients with chronic *Chlamydia*-induced ReA, and they are not recommended.

(ii) Antibiotic trials in enteroarthritis. Several reports on the short- and long-term use of antibiotics on enteric ReA have

TABLE 12. Evidence of the role of long-term antibacterial treatment in ReA

Reference	Study design	No. of patients and diagnosis	Intervention	Results
150	Open (no control group)	10 *C. trachomatis* ReA	3-mo treatment with minocycline	Improvement in clinical parameters (pain, morning stiffness, Schobert, etc.)
113	Double-blind, randomized	40 ReA (21 *Chlamydia* ReA, 17 entero-ReA)	3 mo, 21 patients given lymecycline and 19 patients given placebo	Favourable effect in chlamydia-induced ReA but not in other groups
108	Follow-up	17 ReA (9 lymecycline group, 8 placebo group)	Follow-up 10 yr after the index attack of ReA	Treatment strategy at the acute index attack had no major effect on the outcome
222	Double-blind, randomized	32 Chamydial ReA	2 wk vs 4 mo of doxycycline	Long-term treatment is not superior to short-term treatment
181	Double-blind, randomized	116 ReA (104 uro-ReA)	Ciprofloxacin vs placebo for 3 mo	No difference in outcome between ciprofloxacin and placebo treatment
203	Double-blind, randomized	36 patients chronic ReA (32 entero ReA, 4 Chlamydial ReA)	Ciprofloxacin vs placebo for 3 mo	No definite advantage of ciprofloxacin
229	Double blind, randomized	71 acute ReA (60 entero-ReA, 11 uro-ReA)	Ciprofloxacin vs placebo for 3 mo	No differences in efficacy variables at 12 wk
230	Follow-up	53 ReA (mostly entero-ReA) (26 ciprofloxacin group, 27 placebo)	Follow-up 4–7 yr after the initial ReA	Treatment in acute phase may prevent the development of chronic rheumatic diseases (especially in HLA-B27)

shown no beneficial effect on either the development of ReA or its outcome (177).

Antibiotic treatment of acute *S. enterica* serovar Enteritis does not prevent the occurrence of arthritis. Of interest, a study carried out with 126 participants of a radiology symposium in Sweden who contracted *S. enterica* serovar Enteritidis infection showed that 108 individuals developed enterocolitis and 17 developed ReA. Of the 126 individuals, 58% received antibiotics (ciprofloxacin, norfloxacin, doxycycline, co-trimoxazole, or pivmecillinam-pivampicillin, for an average of 9 days) for the intestinal infection. A total of 10 of 65 treated patients and 7 of 48 untreated patients reported joint symptoms (123). A similar negative experience was reported after a large single-source *S. enterica* serovar Bovismorbificans outbreak (134).

Frydén et al., in a non-blinded, prospective study of 40 patients with enteroarthritis secondary to multiple agents including *Y. enterocolitica*, *Salmonella*, or *Campylobacter* and randomized to treatment with or without antibiotics, also observed no differences concerning the duration of arthritis, degree of inflammation, number of joints affected, or laboratory results between those treated and not treated with antibiotics (55).

Control studies of long-term antibiotic therapy (3 months) with tetracycline or ciprofloxacin in patients with enterobacteria-induced ReA have failed to demonstrate a beneficial effect of antibiotic treatment over placebo (113, 181, 203, 229) during the acute phase of ReA. Yli-Kerttula et al., however, have just reported their study of the effect of a 3-month course of ciprofloxacin on the late prognosis of ReA. They found that their ReA patients, 4 to 7 years after the initial diagnosis and following a 3-month course of ciprofloxacin given in the acute phase of the disease, fared better than those given placebo. Their findings suggest that antibiotic-treatment may prevent chronic consequences of ReA, especially in HLA-B27 positive subjects (230).

In an animal model of *Yersinia*-induced arthritis, ciprofloxacin treatment was shown to reduce the incidence of arthritis only when given immediately after injection and before or shortly after the onset of clinical symptoms. This finding is of little clinical relevance, since patients are rarely seen early in their disease. In this animal model, late antibiotic treatment had no beneficial effect (199).

Taken together, the evidence seems to indicate that neither short-term nor long-term antibacterial treatment of enteric infection-related ReA has a place in the management of this disorder.

Refractory ReA: second-line therapy. As already discussed, only a minority (fewer than 20 to 25%) of patients with ReA fail to respond to NSAID therapy. A more aggressive therapeutic approach is used in this situation and includes the use of the so-called second-line agents or disease-modifying antirheumatic drugs (DMARDs). Firm evidence about the use of second line agents in ReA is lacking, and most available studies in the literature have a small sample size and an uncontrolled design and are of short duration (161).

Sulfasalazine may exert beneficial effects in ReA patients by either diminishing existing mucosal inflammation through inhibition of NF-κB, by reducing mucosal permeability to foreign antigens, or by acting directly on the inflamed joint (119). It should be added that it may also have antibacterial activity (47). In two early non-blinded studies, a small number of patients (15 and 18 patients) who had not responded to NSAID therapy were given sulfasalazine for an average of approximately 3 months. A long-lasting remission of their ReA was observed in both studies, even after the sulfasalazine therapy was discontinued. No significant adverse events were reported (139, 207). A large multicenter study conducted by the Department of Veterans' Affairs in patients with a chronic mean ReA duration of 10 years and unresponsive to conventional therapy demonstrated that sulfasalazine (2 g/day) is well tolerated and effective in treating ReA (34). A reanalysis of the same study published by the same study group showed different responses to sulfasalazine in patients with axial or peripheral involvement (33).

Methotrexate is widely used with good effect (112). The absence of controlled studies of ReA, however, weakens some of the evidence gathered. In patients with spondylitis, methotrexate may prevent peripheral-joint destruction and axial ankylosis as determined by radiographic evaluation (161).

Azathioprine efficacy in treating peripheral arthritis when given at 1 to 2 mg/kg has been shown in a placebo-controlled trial (171). A variety of other second-line agents or DMARDs including cyclosporine, leflunomide, gold salts, cyclophosphamide, bromocriptine, 6-mercaptopurine, and levamisole have been used with benefit in treating chronic ReA. Controlled studies, however, are not available (37).

Of particular interest is the use of TNF-α inhibitors in the management of ReA. Control studies are lacking, but pilot studies and single case reports suggest that they may also be extremely effective in the chronic phases of ReA. The use of TNF-α inhibitors in patients with ReA raises a number of issues that await further resolution. TNF-α is a key component in our defense against infectious microorganisms, and the use of these agents in an infection-related disorder may appear inappropriate. Its use in HIV-related ReA has been followed by dramatic clinical improvement of some manifestations, although it resulted in sepsis and death in a patient (30, 58). It should also be kept in mind that ReA is a Th2-related disorder and, as has been shown in early ReA (duration of less than 8 weeks), peripheral blood mononuclear cells secrete less TNF-α on mitogenic stimulation (compared with early untreated RA) (30). Furthermore, ReA patients with a lower TNF-α secretion have a longer disease duration than do patients with higher secretion. Based on these issues, we think that TNF antagonists should be a therapeutic alternative only for patients refractory to conventional therapy. Further studies are needed to assess the proper place of these antagonists in our therapeutic armamentarium for ReA.

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