Interplay of environmental triggers and host response in reactive arthritis: can we intervene?

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Reactive arthritis (ReA) is an inflammatory process triggered by certain Gram-negative bacteria, with *Chlamydia trachomatis* being the most common cause. The pathophysiology of ReA represents the classic interplay between environment (infectious agents) and host responses. The host responses are, at least in part, governed by genetics. These bacteria or bacterial products are trafficked to the target organs, such as the synovial tissue. The bacterial persistence and ensuing inflammatory response lead to the pathogenic sequelae of ReA. This entire process represents a delicate balance of the major histocompatability complex, cellular uptake of the pathogens, chemokine regulation, Toll-like receptors and T-helper (Th)1 versus Th2/Th3 responses. Therapy has had limited success. As our knowledge of the pathophysiology of ReA continues to grow, our therapies can become more focused and efficacious. This review will devote special attention to *Chlamydia*, since it is the most common cause of ReA.

Crossroads of environment & genetics

Chlamydia trachomatis, *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia* and, to a lesser degree *Chlamydia* (*Chlamydophila*) *pneumoniae* are all known triggers of reactive arthritis (ReA). The pathophysiology of ReA is the classic model of interplay between environment, genetics and host responses. The causative organisms are Gram-negative, with lipopolysaccharide (LPS) as a key component of their cell wall. While we are beginning to understand aspects of the bacterial products and their effects during infection, we have very little understanding of the host's response to those products.

The human leukocyte antigen (HLA)-B27 plays a role in the pathophysiology of the spondyloarthropathies (SpAs). However, compared with ankylosing spondylitis (AS), it is less important in the development of ReA. The HLA-B27 prevalence in previous ReA studies has ranged from 46 to 80% [1–6]. Since the symptoms of ReA may be subtle (particularly with chronic ReA), it is possible that the true prevalence of HLA-B27 in ReA may even be lower. While the debate on the true role of HLA-B27 as it relates to the SpAs continues, this discussion will focus on the bacterial products associated with ReA and the host response that includes, but is not dependent on, HLA-B27. Special attention will be given to *Chlamydia*, since this is the most common cause of ReA.

Triggering organisms persist

PCR technology has occasionally demonstrated the presence of chromosomal DNA from the known triggers of ReA in the synovial tissue of patients with the post-dysentery form of ReA [7–9]. This same technology has demonstrated the routine presence of both *C. trachomatis* and *C. pneumoniae* in the synovial tissue of patients with post-chlamydial arthritis [10–12]. One important difference is that these chlamydiae exist in a persistent metabolically active state, whereas the post-enteric organisms do not, with the possible exception of *Yersinia* [13]. Other bacterial products have been observed in the synovial tissue of patients with various types of arthritis, and thus the importance of this finding has been questioned [13–15]. Conversely, the well-documented finding of viable *Chlamydia* highlights an important potential difference in the pathophysiology of ReA.

It has been demonstrated that the persistent form of *Chlamydia* exists in a morphologically aberrant but metabolically active, viable state [10,12,16]. It is different from the elementary bodies (infectious extracellular stage) and the reticular bodies (noninfectious intracellular stage). The pattern of gene expression is significantly different than that observed during normal active infection. For example, expression of the major outer membrane protein (*omp1*) gene (Ct681) and several genes required for the cell division process are severely downregulated during persistence. This is coupled with differential regulation of the three paralog genes specifying *C. trachomatis* heat-shock proteins (HSP)60 (Ct110, Ct604 and Ct755) [16]. *In vivo*, synovial cells which are infected with persistent *C. trachomatis* display moderate upregulation of Ct110, significant upregulation of Ct604 and

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future medicine

downregulation of Ct755. The principal host cell *in vivo* for persistent synovial Ct is the macrophage. Furthermore, there is differential expression of these HSP60 paralogs when comparing *in vitro* and *in vivo* samples (peripheral blood mononuclear cells [PBMCs]) in persistent infection [16]. Ct110 is downregulated *in vitro* in infected monocytes, but it remains persistently elevated *in vivo* in synovial cells. Ct604 is significantly upregulated both *in vitro* and *in vivo.* Lastly, Ct755 transcription is downregulated both *in vitro* and *in vivo* in persistently infected cells. Another important Ct-specific gene that is upregulated during persistence *in vitro* and *in vivo* is Ct414 [17].

This process is regulated, at least in part, by the heat-inducible transcription repressor (hrcA) protein. HrcA is a transcriptional repressor that regulates stress response genes in many bacteria by binding to the CIRCE operator. In *C. trachomatis* infections, hrcA governs Ct110 production. Monocytes infected *in vitro* with *C. trachomatis* display high levels of *hrcA* gene expression, and *in vivo* synovial cells display low levels [18].

It is important to remember that the aforementioned findings apply only to *C. trachomatis* and not *C. pneumoniae*. There are differences even within the *Chlamydia* genus. Differences in cytokine and chemokine mRNA profiles have been demonstrated in human synovial tissue chronically infected with *C. trachomatis* and *C. pneumoniae* [19]. Furthermore, a detailed gene expression profile of intracellular viable *C. trachomatis* and *C. pneumoniae* revealed different transcriptional response, which was no longer present when the organisms were ultraviolet inactivated [20]. These differences suggest more than innate immunity is involved and may explain the apparently higher risk of ReA with *C. trachomatis* as opposed to *C. pneumoniae*. It is important to remember that, although we are beginning to describe the gene pattern of persistent *Chlamydia*, the genome of *C. trachomatis* and *C. pneumoniae* encodes literally hundreds of unknown proteins that could be of immunological importance.

HSPs are paramount to the persistent state of both *C. trachomatis* and *C. pneumoniae*. They provide many functions, and they are integral in a cell's defense mechanism. HSPs are conserved molecules synthesized by both prokaryotic and eukaryotic cells, and they are known to play an essential role in protein folding, assembly and translocation. Under stressful conditions, HSPs enable cells to survive lethal assaults by preventing protein denaturation [21]. Hsp60 has also been shown to be pivotal in the inability of *Chlamydia*-infected cells to undergo apoptosis [22,23]. These molecules also have a potential role in conferring antibiotic resistance [24,25], and are thought to be potentially immunogenic [26]. Therefore, elimination of the HSPs is likely to be important in abrogating the pathogenic sequelae of *Chlamydia*-induced ReA, either by eliminating the immunogenic nidus itself or rendering the infected cell more susceptible to apoptosis and, subsequently, to therapy.

Host response to triggering organisms

While we are beginning to understand the relation of the bacterial products to chlamydial persistence, there is less information about the host response to these persistent organisms. The same is true for the presence of bacterial DNA in the synovium of patients with the post-dysentery form of ReA. We are beginning to answer these questions:

- How do these bacteria enter the cell?
- What factors traffic them to the joints and other target organs?
- What enables them to enter this persistent state (at least with *Chlamydia)*?
- Is their presence in the affected organs merely a trigger for an autoimmune response, or do these organisms indeed represent the nidus for the inflammatory process?

As stated, a persistent viable state has been established for *C. trachomatis* and *C. pneumoniae*. This may also be true for *Yersinia*. Bacterial DNA from the other post-dysentery organisms has been demonstrated in the synovial tissue. This phenomenon of host tolerance is likely to be multifactorial in nature.

HLA-B27 antigen

Since HLA-B27 is a class I histocompatability antigen, the focus of its role in the pathophysiology of ReA has been antigen presentation. It has been postulated that HLA-B27 presents arthritogenic microbial peptides to T cells stimulating an autoimmune response, so-called molecular mimicry. A previous study has demonstrated a high degree of conservation in the T-cell responses obtained from the synovial fluid of patients with recent ReA, irrespective of the triggering organism [27]. In this same study, $CD8^+$ synovial cells reacted toward several B*2705 lymphoblastoid cell lines. Although intriguing, this study only analyzed four patients with ReA.

Conversely, B27 itself may serve as the autoantigen that is targeted by the immune system. It is possible that exposure to the triggering bacteria may alter tolerance to the B27 antigen. Animal data exist to support this theory. Unlike their wild-type counterparts, HLA-B27 transgenic rats are tolerant of B27 immunization using either $B27^+$ splenocytes or plasmid DNA. However, if these same splenocytes are exposed to *Chlamydia in vitro*, a cytotoxic response is generated [28]. No such response was generated with targets transfected with control B7, B14, B40, B44 or HLA-A2. Thus, self-tolerance to B27 may be subverted by *Chlamydia* and possibly by the other Gram-negative triggering bacteria.

Furthermore, the role of HLA-B27 may, at least in part, function outside of antigen presentation. It has been suggested that HLA-B27 enhances the invasion of *Salmonella* into human intestinal epithelial cells [29]. It has also been suggested that *Salmonella* invasion leads to significant recognizable changes in the B27-bound peptide repertoire [30]. However, a similar study found only minimal changes in the peptide repertoire [31]. Invasion of *Chlamydia* may not be altered by HLA-B27, but intracellular replication and formation of inclusion bodies might be suppressed by the cytoplasmic tail of this antigen [32]. If true, this could predispose the cell to chlamydial persistence. Conversely, it has been suggested that HLA-B27 has no influence on invasion or replication of *C. trachomatis* serovar L2 within cell lines [33]. Recent data suggest that HLA-B27-restricted epitopes derived from proteoglycans, specifically human aggrecan, serve as autoantigens and are involved in the inflammation that is characteristic of the SpAs and ReA [34]. Perhaps there is only a threefold certainty for the role of HLA-B27 in the pathophysiology of ReA: it is complex, undefined and not the sole determinant.

Cellular uptake

It is clear that the causative organisms of ReA are incorporated into peripheral blood mononuclear cells. These same organisms persist intracellularly in synovial cells. The majority of these data apply to *Chlamydia*, both *C. trachomatis* and *C. pneumoniae*. What governs this intracellular uptake is less apparent. Chlamydial infection, specifically, is initiated when the elementary body (EB) binds to the target eukaryotic cell. There is no known cell surface receptor tunique to *Chlamydia* or the other causative organisms of ReA. Toll-like receptor (TLR)-4, which will be discussed below, recognizes LPS. LPS, which is contained in the cell walls of all causative organisms. However, there is no evidence suggesting that TLR-4 is involved in the intracellular processing of these organisms or bacterial products. There are some data which suggest the EB of both *C. trachomatis* and *C. pneumoniae* interacts with host cell surface glycosaminoglycans during cellular uptake [35]. However, following invasion, the *C. trachomatis* was confined to distinct vacuoles that did not develop into characteristic inclusion bodies. Recently gathered evidence suggest that *C. trachomatis* and *C. pneumoniae* EBs do not attach directly to the low-denisty lipoprotein (LPL) receptor on the host cell, rather apolipoprotein (Apo)E which is adherent to the surface of the EB attaches to the host cell LDL receptor family carrying the EB with it [36]. This could represent a truly remarkable adaptation of *Chlamydia* utilizing a basic cellular function involving cell homeostasis as its pathway to host cell attachment and uptake.

Chemokine involvement

After the causative bacteria are acquired, they disseminate to the synovial tissue and other target organs. Chemokines and chemokine receptors regulate leukocyte recruitment into inflamed tissues. CCR1 and CCR5 have become of interest because of their role in recruiting T helper (Th)1 type T cells under inflammatory conditions [37]. A recent study discovered increased expression of CCR1, CXCR4 and CCR5 in the synovial tissue of patients with several types of arthritis including ReA [38]. However, there was no apparent unique chemokine profile related to ReA compared with the other types of arthritis studied.

Toll-like receptors

The TLRs recognize extracellular pathogens and activate immune cell responses as part of the innate immune system. TLR-4 recognizes LPS, thereby potentially playing a role in the pathophysiology of ReA. Recent mice data have demonstrated that effective host clearance of *C. trachomatis* depends on appropriate TLR-4 expression by neutrophils [39]. TLR-4-deficient mice exposed to *Salmonella* demonstrate dramatically increased bacterial growth and increased demise [40]. Certain polymorphisms of TLR-4 have been associated with Gram-negative infections as well as Crohn's disease and ulcerative colitis, two inflammatory conditions related with the SpAs [41–43]. However, these same polymorphisms do not appear to confer risk of ReA [44].

Th1 versus Th2/Th3 response

The interplay of HLA-B27, chemokines, TLRs, cellular uptake and bacterial persistence contributes to the pathogenesis of ReA (Box 1). How all of these link together is still unknown. It is possible that the common ground is at a very rudimentary level, specifically, the Th1 versus Th2/Th3 response. Rather a large amount of data support the role of Th1 cytokines, particularly tumor necrosis factor (TNF)α, in the pathogenesis of the SpAs. While these same cytokines play a role in ReA, there may be more of a predilection for the Th2 response compared with the other SpAs. This might be particularly certain for the chronic form of ReA. Furthermore, the Th3 response might also be instrumental in chronic ReA. Two factors must be considered regarding the exact role of the Th1, Th2 and Th3 pathways in ReA: the relative role and timing of each response.

The Th1 cytokine, TNFα, has been measured in the peripheral blood of patients with ReA. Compared with patients with rheumatoid arthritis, ReA patients demonstrated significantly lower levels of TNFα [45]. Furthermore, patients who were HLA-B27 positive or had disease duration of greater than 6 months secreted significantly less TNFα in their peripheral blood. Similar findings have been demonstrated in the joints of patients with ReA; specifically higher levels of interelukin (IL)-10 and lower levels of TNFα and interferon (IFN)γ (favoring a Th2 profile) [46,47].

The Th2 profile predilection observed in ReA probably plays a role in bacterial persistence. *In vitro* data have demonstrated that background cytokine levels are important in maintaining the persistent state of *C. trachomatis* and *C. pneumoniae*. Specifically, low levels of TNFα and IFNγ help to promote this persistent state [48–51].

Box 1. Bacterial persistence as it relates to reactive arthritis.

Post-dysentery ReA

- Chromosomal DNA from *Salmonella*, *Shigella*, *Campylobacter* and *Yersinia* have been detected using PCR technology from synovial fluid or synovial tissue of patients with various arthritidies [7–9,13–15].
- The majority of these samples came from patients with undifferentiated spondyloarthropathies (SpAs) or reactive arthritis (ReA) [7–9,13–15].
- Only one study has suggested viable bacteria (*Yersinia)* in the synovial fluid/tissue [13].
- Therefore, the majority of the data suggest that only bacterial fragments traffic to the affected tissues.

Post-chlamydial ReA

- PCR technology has routinely demonstrated the presence of persistent viable *Chlamydia* in the synovial fluid/tissue of patients with ReA [10–12].
- This same finding has occasionally been demonstrated in patients with undifferentiated SpA or other types of arthritis [15].
- The pattern of gene expression is significantly different in the persistent state compared with that observed in an acute infection [16].
- Gene expression present in persistent viable *Chlamydia trachomatis* [16]:
  - Major outer membrane protein (*omp1* [Ct681]) and several genes required for cell division are severely downregulated.
  - Differential regulation of three paralog heat-shock protein-60 genes (*Ct110*, *Ct604* and *Ct755*).

In vivo *(synovial tissue)*

- *Ct110*: moderate upregulation [16].
- *Ct604*: significant upregulation [16].
- *Ct755*: downregulated [16].

In vitro *(peripheral blood mononuclear cells)*

- *Ct110:* downregulated [16].
- *Ct604*: significant upregulation [16].
- *Ct755*: downregulated [16].
- *Ct110:* expression is governed (at least in part) by the hrcA repressor protein [18].
- *Ct414:* is upregulated during persistence *in vitro* and *in vitro* [17].
- Chlamydial heat-shock protein 60 genes play a role in resisting apoptosis of infected cells, conferring antibiotic resistance and are potentially immunogenic [22–25].

Table 1. Treatments for reactive arthritis.

Treatment	Prospective trials (n)	Efficacy	Concerns
Nonsteroidal anti-inflammatory drugs	No	Mild to moderate	Gastrointestinal toxicity, bleeding, hepatic, renal and possible increased risk of thromboembolic events
Corticosteroids	No	Moderate to very good	Diabetes, hypertension, osteoporosis, glaucoma, cataracts and avascular necrosis; side effects prohibit long-term use and possible worsening of bacterial persistence
Sulfasalazine	Yes (1) [57]	Moderate	Anemia, rash and gastrointestinal distress
Methotrexate	No	Moderate	Hepatotoxicity and bone marrow suppression and alveolitis
Azathioprine	No	Unclear	Bone marrow suppression and hepatotoxicity
Cyclosporine	No	Unclear	Renal toxicity; bone marrow suppression
Tumor necrosis factor-α antagonists	One small open-label study (ten patients with ReA and undifferentiated spondyloarthritis) [58]	Moderate	Infections, cost, possible increased risk for malignancy and possible exacerbation of bacterial persistence
Antibiotics	Yes (9) [5–10,62,64,70]	Unclear	Antibiotic resistance

As stated, temporal relationships of these different Th1 and Th2 cytokines may also be important in disease manifestations and maintenance (i.e., more chronic disease is inversely associated with Th1 cytokine levels). The same may hold true for disease initiation. A recent study analyzed a *Chlamydia*-induced arthritis rat model and found that susceptible rats mounted a lesser initial TNFα, IFNγ and IL-4 response to their *Chlamydia* infection [52]. Therefore, lower initial responses of these Th1 cytokines may increase the likelihood of developing ReA compared with patients who are exposed to the causative organism, but do not develop ReA.

Other data have suggested a role for the Th3 response. $\gamma\delta^+$ synovial-based T cells from three patients with ReA predominantly expressed transforming growth factor β2 and granulocyte monocyte-colony stimulating factor [53]. Compared with $CD4^+$ and $CD8^+$ T cells from the same patients, they expressed a more heterogenous cytokine profile that favored the Th3 response.

Thus, the overall cytokine expression and T-cell response in patients with ReA appears to favor that of a Th2 and possibly a Th3 response, with a lesser role for Th1 cytokines. Perhaps the Th1 cytokines are responsible for the clinical manifestations, and the Th2 and Th3 pathways contribute to disease chronicity. Clinically, this is borne out by the most severe manifestation occurring early and more chronic disease with subtle findings. Slight perturbations of this Th1 and Th2/Th3 balance might also explain the waxing and waning manifestations of chronic ReA.

Can we intervene?

ReA is one of the few arthritidies for which we know of a defined trigger. Since we know the initial cause, the quest to define the interplay of these environmental triggers and host responses is seductive. Although our knowledge of the pathophysiology which underlies this disease process continues to unfold, the ideal treatment remains elusive (Table 1). Each of the separate pathophysiological processes described above represents a potential option for a therapeutic intervention. The TNFα antagonists could intervene in this disease process; however, there are theoretical and practical concerns with this treatment approach. Since ReA is caused by Gram-negative bacteria and there is evidence of viable bacterial persistence in the target organs of affected individuals, antibiotics may also be a treatment alternative. To date, the results of such trials have been equivocal; however, the data are more encouraging with *Chlamydia*-induced ReA, specifically. Finally, data are limited regarding a more general approach to treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) or disease-modifying antirheumatic drugs (DMARDs) more often used to treat other inflammatory arthritidies. These treatments will be discussed, focusing on more relevant findings related to pathophysiology with an eye towards the future.

NSAIDs are generally employed as first-line treatment in ReA, but their success is limited and there are no well-designed trials to support their use. There has been a trial evaluating the utility of sulfasalazine in ReA [54]. This trial of 134 subjects

demonstrated improvement in 62% of the participants compared with 47% on placebo. Methotrexate, azathioprine and cyclosporine have been advocated as potential treatments, but never formally evaluated in a prospective trial.

While the TNFα antagonists have demonstrated great success in the treatment of other types of SpAs, there are no trials in ReA. However, a small open-label study and case reports have suggested modest benefit with these drugs in the treatment of ReA [55–57]. In the open-label study with etanercept, there were five patients who were PCR-positive for *Chlamydia* at some time during the observation period. Of the five, three were PCR-positive in the synovium for *C. trachomatis* before treatment. Of these three, two of the patients were PCR-negative upon receiving therapy, and one remained positive. Furthermore, two patients with negative PCR results at baseline became PCR-positive for *C. pneumoniae* while on etanercept. These equivocal results do not dissuade the theoretical concerns that exist regarding the use of these drugs in ReA. As previously mentioned, lower levels of TNFα have been associated with ReA compared with other types of inflammatory arthritis, particularly with established disease. Furthermore, low initial levels of TNFα after initial exposure to the causative organism may predispose to disease development. Additionally, ReA is thought to be more of a Th2/Th3-driven disease. Could exposure to a TNFα antagonist exacerbate this process?

The persistent viable state which has been demonstrated with *Chlamydia* also suggests caution regarding the use of TNFα antagonists. *In vitro* data have convincingly demonstrated that the levels of persistent *Chlamydia* are inversely associated with TNFα (and IFNγ) levels [48–52]. What happens to the *in vivo* synovial bacterial load of *Chlamydia* in patients who are exposed to these drugs? This question must be explored.

Interestingly, however, patients with chronic ReA have been shown to exhibit high production of TNFα and IFNγ which appears to support the use of TNFα antagonists [58].

The exact role of antibiotics as a treatment for ReA remains to be fully defined. An early trial assessing 3 months of treatment with lymecycline demonstrated no benefit to patients with post-dysentery ReA, whereas there was improvement in patients with *Chlamydia*-induced ReA in this same trial [1]. A subgroup analysis of another previous trial studying ciprofloxacin as a treatment for ReA suggested benefit in post-chlamydial patients with no such improvement in the other patients [4]. Other studies assessing doxycycline, ciprofloxacin and azithromycin in ReA failed to demonstrate benefit, but there was no effort to separate post-chlamydial patients [2,3,5,59]. Interestingly, a follow-up of one of the aforementioned ciprofloxacin trials suggested that this antibiotic significantly improved long-term prognosis [60]. Finally, another study suggested significant improvement in patients with post-chlamydial ReA with a combination of knee synovectomy and 3 months of azithromycin [61]. Therefore, it appears that there may be benefit in the post-chlamydial form, but not ReA, that is secondary to the post-dysentery organisms. The observation of viable metabolically active *Chlamydia*, and the general lack of viable post-dysentery organisms, in the synovial tissue of patients with ReA support this finding.

The complexity of antibiotics as a potential treatment for *Chlamydia*-induced ReA runs even deeper. The persistent viable state of *Chlamydia* is very different to that of an acute *Chlamydia* infection. This aberrant state includes the differential gene protein expression, including the different HSP60 paralogs, previously described. Therefore, it is likely that the most effective antimicrobial therapy would be different from that of a typical acute localized infection with this same organism.

In vitro data have demonstrated that intracellular chlamydiae are driven into a persistent state when exposed to chronic monotherapy with several antibiotics, including doxycycline, azithromycin and ciprofloxacin [62–65]. *In vitro* evidence also exists to suggest that rifampin monotherapy can induce resistance in *Chlamydia* infections [67]. These data suggest that chronic monotherapy with the aforementioned antibiotics would be unlikely to eradicate the persistent infection. Indeed, this might explain some of the negative clinical trial data that have assessed antimicrobial monotherapy in this setting [2–5,59].

Since HSPs are known to block cells from lethal assaults in general, and resist apoptosis in cells with a persistent *Chlamydia* infection, specifically, it is possible that attenuation of chlamydial HSP60s is paramount in eradicating this persistent chlamydial state. Rifampin has been demonstrated to block all transcripts in *C. trachomatis* infections, including HSPs [66]. This antibiotic binds to the β-subunit of prokaryotic RNA polymerase and prevents initiation of transcription of HSPs.

Interesting *in vitro* data suggest successful synergistic eradication of cells infected with *Chlamydia* with a combination rifampin and

azithromycin [63]. However, in this same study, monotherapy with both of these same antibiotics did not eradicate the persistent infection. A recent study revealed significant improvement in patients with presumed *Chlamydia*-induced ReA after 9 months of a combination of rifampin and doxycycline compared with doxycycline monotherapy [67]. Additionally, the aforementioned trial assessing knee synovectomy and 3 months of azithromycin in post-chlamydial patients revealed remission in 15 of 20 patients [62]. Subsequent treatment with a combination of antibiotics achieved remission in four of the remaining five patients. Therefore, it is possible that a prolonged combination of antibiotics may eradicate the persistent state of *Chlamydia* along with its pathogenic sequelae. Rifampin might be a necessary component of this combined therapeutic approach. This area deserves further study.

Future perspective

The triggering bacteria are well defined. Trafficking to the joint of all of the causative organisms is proven. Chlamydial persistence is well described. Host responses are just now beginning to be understood. Can we intervene in this process of environment and immune response? Unfortunately, we have not established definitive proof.

Several steps in the pathophysiological process are attractive targets. Inhibition of the cellular uptake of the causative organisms, chemokine inhibition and cytokine intervention which would alter the Th1 verus Th2/Th3 response are all attractive potential targets for the future. Another strategy might be vaccines against these organisms. However, a potential problem with a *Chlamydia* vaccine, specifically, relates to those individuals who already harbor persistent *Chlamydia*. Could a vaccine exacerbate the symptoms in these patients? Furthermore, several vaccines would have to be developed against all of the causative organisms in order to eradicate ReA.

The most immediate therapies which might have a significant impact on disease activity include the TNFα antagonists and combined antimicrobials. The latter probably only applies to *Chlamydia*-induced ReA, specifically. Since TNFα appears to be involved in the pathophysiology of ReA, TNFα antagonism could ameliorate the symptoms. However, these same drugs might also promote bacterial persistence.

Although the clinical symptoms of post-dysentery and post-chlamydial ReA are the same, it is probably best to separate these two disease entities based on potential therapeutic response. Given the differences in behavior of the causative organisms and the apparent difference in antimicrobial response, the ideal treatment is likely to be different for each triggering organisms.

Conclusion

ReA is unique because it has known bacterial triggers. Our knowledge regarding the interplay of these environmental triggers and human response continues to expand. Data exist to suggest bacterial persistence and trafficking to the joints with all of these triggers. *Chlamydia* appears to be unique, with the possible exception of *Yersinia*, in that it persists in a viable state. We have begun to uncover the gene protein expressions during chlamydial persistence, yet much remains to be learned in this regard. Even more remains a mystery regarding host response to chlamydial persistence.

Although ReA can spontaneously remit, approximately half of these patients develop chronic disease. To date, we do not have a definitive treatment for chronic ReA. Traditional therapies have included NSAIDs, corticosteroids and DMARDs; however, data are lacking to support their use. The TNFα antagonists appear remarkably effective in the other SpAs, but there are very little data regarding these drugs and theoretical concerns exist regarding the treatment of ReA. The exact role of antibiotics is still not defined, but it appears that there might be a role in *Chlamydia*-induced ReA specifically. Recent data also suggest combination antibiotics are more likely to be efficacious than antibiotic monotherapy. As we continue to unfold the delicate balance that enables bacterial persistence, a definitive treatment will likely follow.

Executive summary

Definite bacterial triggers of reactive arthritis

Post-venereal:

- *Chlamydia trachomatis* (most common cause of reactive arthritis [ReA]).

Post-dysentery:

- *Salmonella*, *Shigella*, *Campylobacter* and *Yersinia.*

Executive summary

Probable cause of ReA

- *Chlamydophila (Chlamydia) pneumoniae.*

Bacterial persistence

- PCR technology has demonstrated the presence of chromosomal DNA from the known triggers in the synovial tissue of patients with post-dysentery ReA.
- PCR technology has routinely displayed viable *Chlamydia* in the synovial tissue of patients with ReA.
- These chlamydiae exist in an aberrant yet metabolically active state.
- Chlamydial heat-shock protein (HSP)60 appears to play a pivotal role in this persistently viable state.

Host response

- The importance of human leukocyte antigen (HLA)-B27 in ReA is less than in ankylosing spondylitis.
- The precise role of HLA-B27 is still not clearly defined. Theories include the presentation of arthritogenic microbial peptides, autoantigen activity and enhanced bacterial invasion or intracellular persistence.
- The elementary bodies (EB) of both *C. trachomatis* and *C. pneumoniae* may interact with host cell surface glycosaminoglycans during cellular uptake.
- Apolipoprotein (Apo)E ε4 may play a role in the cellular uptake of *Chlamydia*.
- ApoE that is adherent to chlamydial EB might attach to the low-density lipoprotein receptor of the host cell carrying the EB.
- CCR1 and CCR5 might play a role in bacterial trafficking in ReA.
- Toll-like receptor (TLR)-4 recognizes lipopolysaccharide (LPS), thereby potentially playing a role in ReA.
- T-cell response in ReA favors that of a T-helper (Th)2 and possibly Th3 response compared with other arthritidies.

Therapeutic intervention

- Very few prospective therapeutic trials have been performed in ReA.
- Traditional therapies include nonsteroidal anti-inflammaotry drugs and disease-modifying antirheumatic drugs (sulfasalazine, methotrexate, azathioprine and cyclosporine) (Box 1).
- Tumor necrosis factor (TNF)-α antagonists have demonstrated great promise in the other spondyloarthropathies, but have not been formally evaluated in ReA.
- *In vitro* data demonstrate that levels of persistent *Chlamydia* are inversely associated with TNFα (and interferon-γ). This suggests that caution should be taken with TNFα antagonism as a therapy.
- The role of antibiotics remains to be fully defined. There are no data to suggest a role in post-dysentery ReA, but they may be beneficial in post-chlamydial ReA.
- Combination antibiotics, which also inhibit chlamydial HSP60, might be an efficacious treatment for *Chlamydia*-induced ReA.

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